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CIC-Rearranged Sarcoma of the External Auditory Canal: A Case Report

Running title: CIC-Rearranged Sarcoma of the EAC

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Abstract

Malignant tumors of the external auditory canal (EAC) are rare. Most are carcinomas, predominantly squamous cell carcinoma, whereas sarcomas are exceptionally rare and can pose diagnostic challenges. CIC-rearranged sarcoma is an aggressive undifferentiated round cell sarcoma associated with poor prognosis and limited responsiveness to chemotherapy. To our knowledge, this is the first reported case arising in the EAC. A 36-year-old woman underwent excision of a left EAC mass at another hospital and was referred to our institution after histopathologic examination suggested sarcoma. Imaging demonstrated destruction of the posterior bony canal wall with minimal posterior extension and no nodal or distant metastasis. Lateral temporal bone resection achieved negative surgical margins while preserving the facial nerve, temporomandibular joint, and parotid gland. Histopathologic examination revealed an undifferentiated round cell tumor with nuclear WT1 expression and negative NKX2.2 staining. Next-generation sequencing identified a CIC::DUX4 fusion, confirming the diagnosis. Following multidisciplinary review, adjuvant chemotherapy and radiotherapy were planned because of the risk of recurrence. Adjuvant treatment was ongoing at 3 months after surgery, precluding assessment of long-term outcomes. This case highlights the importance of molecular testing for accurate diagnosis and complete resection with negative margins at the initial definitive surgery for localized, resectable disease. Adjuvant treatment should be individualized, and close long-term surveillance is essential.

Keywords: CIC-rearranged sarcoma, External auditory canal malignant tumor, Undifferentiated round cell sarcoma, Ewing sarcoma

Introduction

Primary malignant tumors of the external auditory canal (EAC) are uncommon. Squamous cell carcinoma is the predominant histologic type, while adenoid cystic carcinoma, basal cell carcinoma, and other malignancies are less common [1, 2]. Sarcomas at this site are exceptionally rare and present diagnostic and therapeutic challenges [1-3]. Histopathologic diagnosis may be difficult because biopsy specimens are often limited and may show changes related to inflammation or previous surgery. In addition, the complex anatomy of the temporal bone can make complete oncologic resection difficult [1, 2]. Molecularly defined undifferentiated round cell sarcomas pose an additional diagnostic challenge because several entities share similar histopathologic features.

CIC-rearranged sarcoma is recognized as a distinct type of undifferentiated round cell sarcoma rather than a variant of Ewing sarcoma. Most tumors harbor CIC::DUX4, generated by fusion of CIC on chromosome 19 with DUX4 on chromosome 4 or 10 [4-7]. These neoplasms predominantly affect adolescents and young adults, usually arise in deep soft tissue, and follow an aggressive clinical course [5, 7-10]. We report a CIC::DUX4-positive sarcoma of the EAC and discuss its pathologic distinction from Ewing sarcoma, the role of molecular testing, and the treatment of localized disease.

Case Report

Clinical History

A 36-year-old woman presented with a mass in the left external auditory canal (EAC). She underwent excision of the lesion with skin grafting at another hospital. Histopathologic examination suggested sarcoma, and she was referred to our institution for definitive diagnosis and oncologic management.

Preoperative Evaluation

Endoscopy demonstrated a lesion occupying the bony EAC (Fig. 1a). Computed tomography showed destruction of the posterior bony canal wall, with only minimal posterior extension (Fig. 1b). Magnetic resonance imaging demonstrated no extension into the surrounding soft tissues (Fig. 1c). 18F-fluorodeoxyglucose positron-emission tomography/computed tomography showed uptake confined to the left EAC lesion, without cervical nodal or distant uptake (Fig. 1d). The tumor was clinically classified as cT3N0M0 according to the modified Pittsburgh classification, which was used to describe the local anatomic extent.

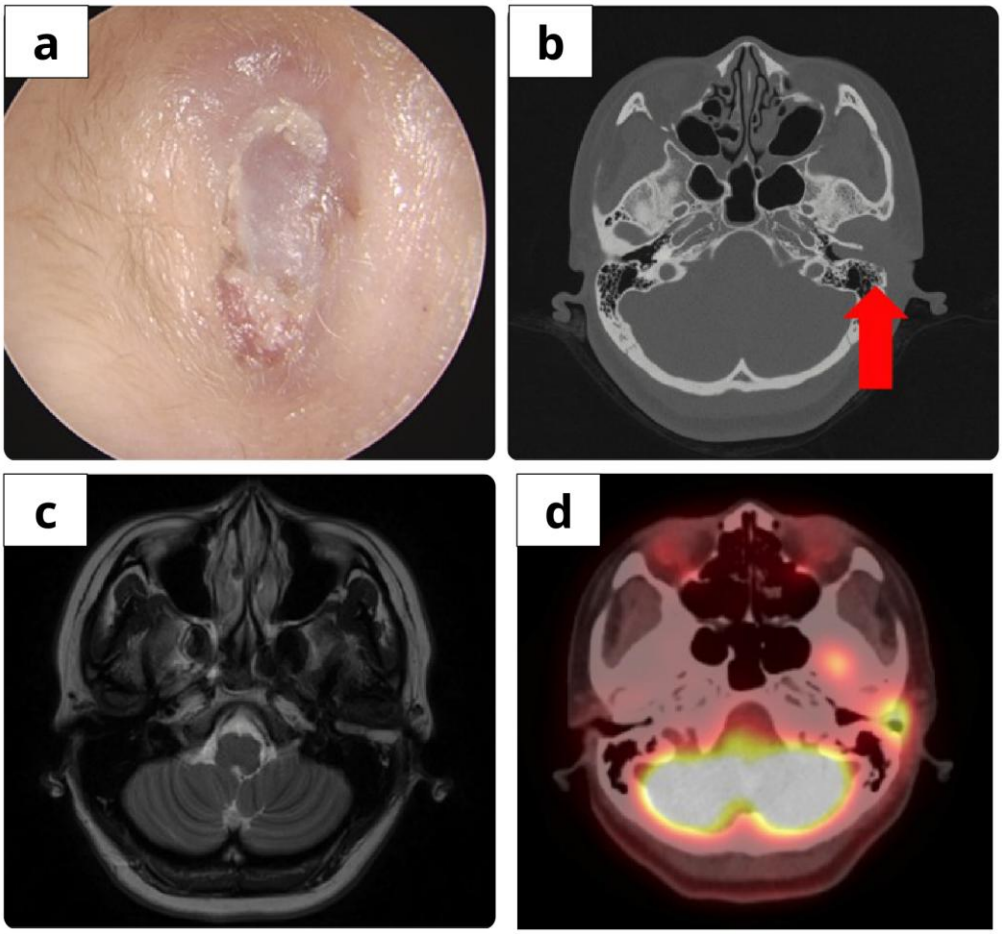


Fig. 1 Clinical and radiologic findings

a Endoscopic image showing a mass occupying the bony left external auditory canal. **b** Axial bone-window computed tomography demonstrating destruction of the posterior bony canal wall (arrow), with minimal posterior extension. **c** Axial magnetic resonance image showing no extension into the surrounding soft tissues. **d** 18F-fluorodeoxyglucose positron-emission tomography/computed tomography showing uptake confined to the left external auditory canal lesion without cervical nodal or distant uptake.

An incisional biopsy of the EAC revealed a malignant undifferentiated round cell tumor. The differential diagnosis included CIC-rearranged sarcoma, Ewing sarcoma, and other undifferentiated round cell sarcomas.

Surgical Procedure

A standard lateral temporal bone resection (LTBR) was performed, with preservation of the facial nerve, temporomandibular joint, and parotid gland (Fig. 2).

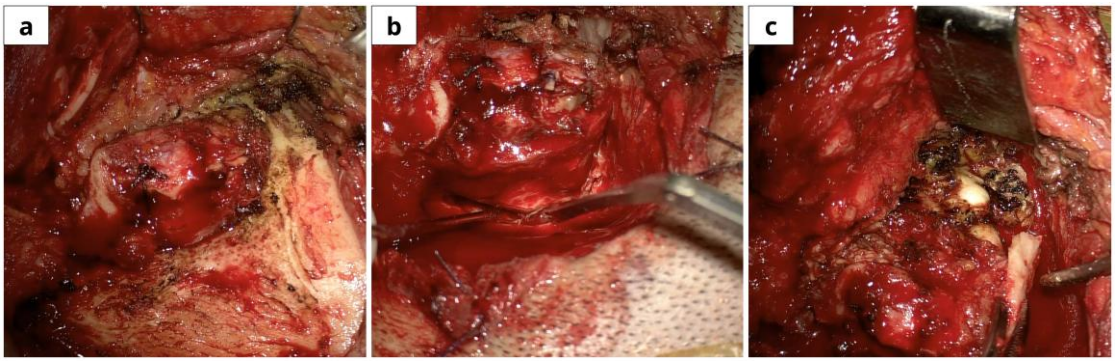


Fig. 2 Representative intraoperative views of the resection planes during lateral temporal bone resection

a The lateral resection line was placed in the cartilaginous external auditory canal. **b** The medial resection plane was established along the lateral aspect of the facial nerve. **c** The anterior resection plane was developed while preserving the parotid gland and temporomandibular joint.

Histopathologic and Molecular Findings

Histologic examination of the resection specimen showed multinodular and lobulated tumor growth separated by fibrous septa (Fig. 3a). At high power, the tumor consisted of undifferentiated round-to-ovoid cells with variable nuclear atypia and conspicuous nucleoli (Fig. 3b). Immunohistochemical staining demonstrated nuclear WT1 expression and an increased Ki-67 proliferation index (Fig. 3c, d). The tumor cells were negative for BCOR, NKX2.2, and NKX3.1, while SATB2 showed no diffuse nuclear expression (Fig. 4a–d). The tumor was classified as Fédération Nationale des Centres de Lutte Contre le Cancer grade 2, and all surgical margins were negative. Next-generation sequencing detected a CIC::DUX4 fusion, establishing the diagnosis of CIC-rearranged sarcoma.

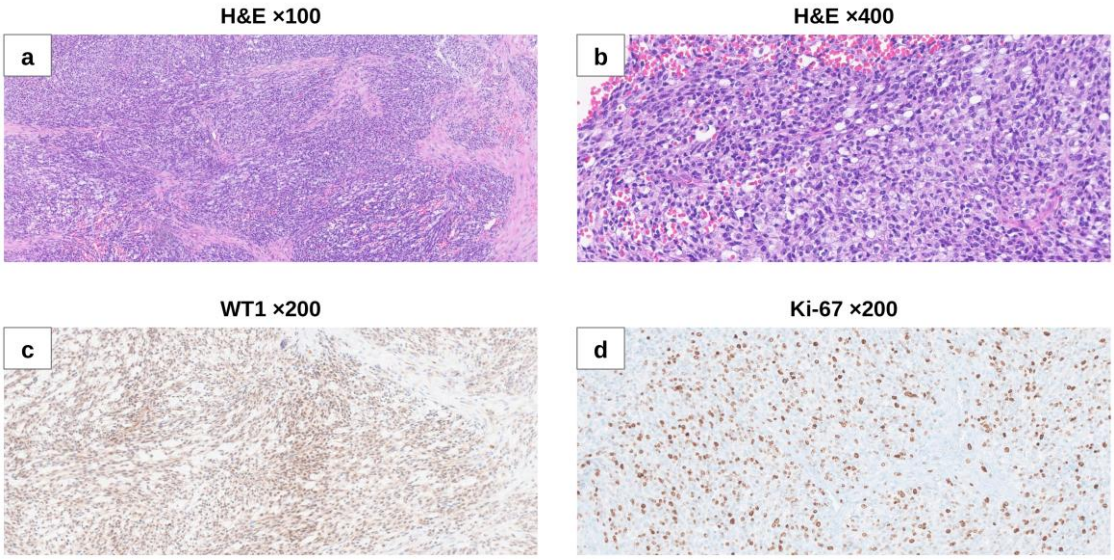


Fig. 3 Histopathologic and immunohistochemical findings in the lateral temporal bone resection specimen

a Multinodular and lobulated tumor growth separated by fibrous septa (hematoxylin and eosin, original magnification ×100). **b** Undifferentiated round-to-ovoid tumor cells with variable nuclear atypia and conspicuous nucleoli (hematoxylin and eosin, original magnification ×400). **c** Nuclear WT1 immunoreactivity (original magnification ×200). **d** Increased Ki-67 proliferation index (original magnification ×200).

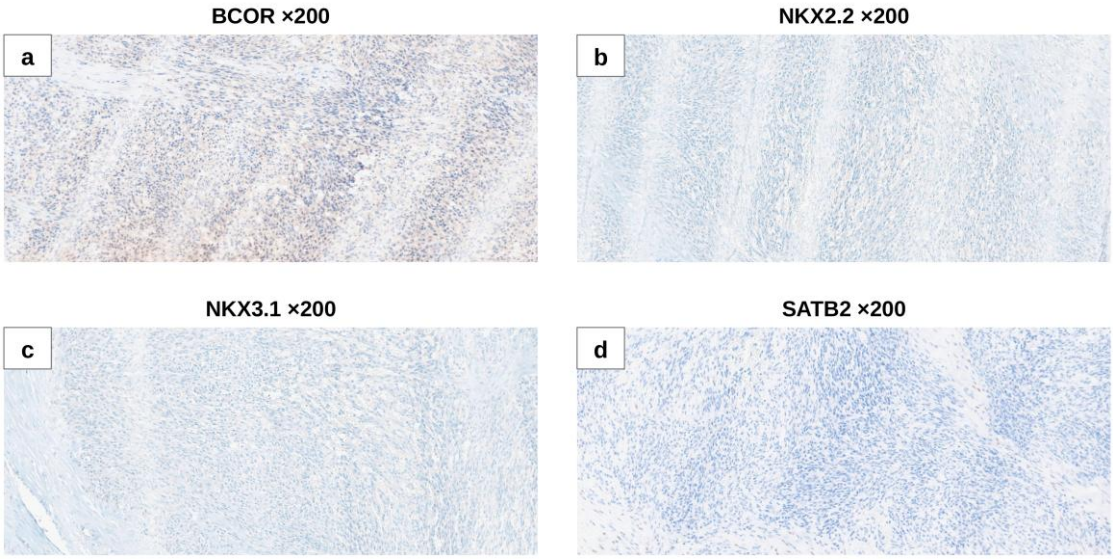


Fig. 4 Immunohistochemical exclusion panel

a No nuclear expression of BCOR (original magnification ×200). **b** No nuclear expression of NKX2.2 (original magnification ×200). **c** No nuclear expression of NKX3.1 (original magnification ×200). **d** SATB2 shows no diffuse nuclear expression, with only rare weakly stained nuclei (original magnification ×200).

Postoperative Course

Following postoperative multidisciplinary review, adjuvant chemotherapy with doxorubicin and ifosfamide (AI) and radiotherapy were planned despite negative surgical margins, in view of the aggressive behavior of CIC-rearranged sarcoma. The planned sequence comprised three cycles of AI, followed by radiotherapy and three additional cycles of AI. At the time of manuscript preparation, 3 months had elapsed since surgery and adjuvant treatment was ongoing.

Discussion

CIC-rearranged sarcoma was historically classified as an "Ewing-like" sarcoma. However, genomic, transcriptional, proteomic, morphologic, and clinical studies have established it as a distinct entity from Ewing sarcoma [4-8, 11, 12]. CIC normally functions as a transcriptional repressor. The CIC::DUX4 fusion retains the DNA-binding specificity of CIC while acquiring a DUX4-derived activation domain, resulting in aberrant activation of ETV-family genes, including ETV1, ETV4, and ETV5 [4, 6, 12]. Experimental models have reproduced the round cell morphology, rapid growth, and metastatic potential of this tumor, supporting a direct oncogenic role of the fusion [12]. Therefore, detection of the characteristic fusion was decisive for the diagnosis in the present case. Histologically, CIC-rearranged sarcoma typically consists of sheets or lobules of round-to-ovoid cells with vesicular chromatin, conspicuous nucleoli, and greater nuclear pleomorphism than classic Ewing sarcoma. Focal spindle or epithelioid morphology and myxoid stroma may also be

present [5, 7, 13-16]. Nuclear WT1 and ETV4 expression can support the diagnosis of CIC-rearranged sarcoma, although these markers are not entirely specific [4, 13, 17]. Nuclear DUX4 is a useful surrogate marker for CIC::DUX4-positive tumors [18-20]. In the present case, the tumor showed nuclear WT1 expression and an increased Ki-67 proliferation index (Fig. 3c, d). BCOR, NKX2.2, and NKX3.1 were negative, while SATB2 showed no diffuse nuclear expression (Fig. 4a–d). The morphology and immunohistochemical findings supported consideration of CIC-rearranged sarcoma and prompted molecular testing. The principal features distinguishing the present tumor, CIC-rearranged sarcoma, and Ewing sarcoma are summarized in Table 1.

Table 1. Differential Diagnosis: CIC-Rearranged Sarcoma vs Ewing Sarcoma

Feature	Present case	CIC-rearranged sarcoma	Ewing sarcoma
Tumor cells	Round-to-ovoid; focal spindle cells	Round-to-ovoid; variable morphology	Uniform small round cells
Nuclei	Pleomorphism and prominent nucleoli	Variable nuclei; prominent nucleoli	Monomorphic; inconspicuous nucleoli
Stroma	Fibrous and focally myxoid	Myxoid stroma may be present	Usually not myxoid
WT1	Nuclear positive	Frequently nuclear positive	Usually negative
CD99	Not performed	Usually patchy or heterogeneous	Strong, diffuse membranous staining
NKX2.2	Negative	Usually negative	Frequently positive
ETV4	Not performed	Frequently nuclear positive	Usually negative
Defining fusion	CIC::DUX4	Usually CIC::DUX4	Usually EWSR1::FLI1

Sources: References 4, 7, 8, 11–13, 20, 21, 24, and 25 in the manuscript.

Molecular testing is important for establishing an accurate diagnosis because morphologic and immunohistochemical findings alone may be insufficient [19, 21]. In the present case, next-generation sequencing identified a CIC::DUX4 fusion, confirming the diagnosis of CIC-rearranged sarcoma. Malignant tumors arising in the EAC or temporal bone are rare. Although other histologic types of sarcoma involving these sites have been reported [1-3], to our knowledge, no previous case of primary CIC-rearranged sarcoma arising in the EAC has been reported. CIC-rearranged sarcomas have been reported in the pharynx and other head and neck soft-tissue sites, but most arise in the extremities or trunk [7, 8, 15].

CIC-rearranged sarcoma follows an aggressive clinical course. Large pathologic series and recent international cohorts have documented frequent local recurrence and distant metastasis, particularly to the lungs, with poorer outcomes than those of Ewing sarcoma [7-10, 14, 22-24]. In a global retrospective study of 148 patients with undifferentiated round cell sarcomas, the 3-year overall survival rate was 39.6% for CIC-rearranged sarcoma, compared with 92.2% for BCOR::CCNB3-rearranged sarcoma [23]. Studies involving children and young adults have similarly shown that localized disease at diagnosis does not eliminate the risk of recurrence [24].

In the present case, the modified Pittsburgh classification was used to describe the local anatomic extent, resulting in a clinical classification of cT3N0M0. Although the modified Pittsburgh classification is commonly used to describe the local extent of EAC malignancies, it was developed primarily for squamous cell carcinoma, and its

prognostic validity has not been established for sarcoma [1, 2]. Therefore, it was used in this case only as a descriptor of local anatomic extent rather than as a validated prognostic staging system for CIC-rearranged sarcoma.

Surgical resection with negative margins remains the primary local treatment for resectable disease [7, 9, 10, 22]. In the present patient, lateral temporal bone resection achieved negative margins while preserving the facial nerve, temporomandibular joint, and parotid gland. Despite negative surgical margins, postoperative multidisciplinary review led to a plan for adjuvant chemotherapy with doxorubicin and ifosfamide and radiotherapy. This decision reflected an individualized assessment of recurrence risk rather than an established CIC-specific adjuvant treatment standard. No adjuvant regimen specific to CIC-rearranged sarcoma has been established. Retrospective studies have included Ewing sarcoma-based chemotherapy and anthracycline- and ifosfamide-based soft-tissue sarcoma regimens [9, 10, 14, 22-25]. Responses in advanced disease are often short-lived, although occasional durable responses to vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide have been reported [9]. However, the available retrospective evidence is insufficient to establish the survival benefit of adjuvant chemotherapy or postoperative radiotherapy after complete resection [9, 10, 22-24].

Current evidence does not support the routine use of molecularly targeted therapy or immune checkpoint inhibitors. Pazopanib and pembrolizumab have not produced

objective responses in the limited reported cases, and durable responses to conventional systemic therapy remain uncommon [9]. Preclinical studies have identified potential dependencies involving the cell cycle, MAPK-related signaling, apoptosis, and transcriptional regulation, but these findings have not yet led to an established CIC-specific therapy [11, 12, 25].

The principal limitation of this report is the short postoperative follow-up of 3 months, during which adjuvant treatment remained ongoing. Therefore, this case cannot establish durable disease control or the efficacy of adjuvant therapy. Published series have documented early local recurrence and distant metastasis, particularly pulmonary metastasis, even in patients with initially localized disease [7-10, 22-24]. These observations support close, long-term surveillance of the operative site and lungs.

Conclusion

To our knowledge, this is the first reported case of CIC-rearranged sarcoma of the external auditory canal. Molecular testing is important for accurate diagnosis. Complete resection with negative margins is considered important for localized, resectable disease, and adjuvant treatment should be individualized. Longer follow-up is needed to assess treatment outcomes and monitor for recurrence or metastasis.

Statements and Declarations

Funding

This study was not supported by any funding.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

Ethical review and approval were not required for this single-patient case report in accordance with institutional policy.

Consent to Participate

Not applicable. This report describes a single patient’s clinical course during routine care.

Consent for Publication

Written informed consent for publication of the patient’s clinical details and images was obtained from the patient.

Availability of Data and Materials

The data supporting the findings of this case report are available from the corresponding author on reasonable request, subject to institutional approval and protection of patient privacy.

Code Availability

Not applicable. No custom code or software application was used for the reported clinical analyses.

Author Contributions

Ichiro Fukumoto and In Seok Moon contributed to the conception and design of the report. Ichiro Fukumoto

collected and interpreted the clinical data and drafted the manuscript. Seung Hyun Jang coordinated with the Department of Pathology and facilitated the acquisition and preparation of the histopathologic images. So Young Ahn contributed to the histopathologic evaluation and preparation of the pathology images. In Seok Moon supervised the study and critically revised the manuscript. All authors reviewed and approved the final manuscript.

References

1. Samara P, Athanasopoulos M, Goulioumis A, Athanasopoulos I (2023) Malignant tumors of the external auditory canal: diagnosis, treatment, genetic landscape, biomarkers, and clinical outcome. Explor Target Antitumor Ther 4(5):801–811. https://doi.org/10.37349/etat.2023.00169
2. Zhong S, Zuo W (2022) Treatment Strategies for Malignancies of the External Auditory Canal. Curr Treat Options Oncol 23(1):43–53. https://doi.org/10.1007/s11864-021-00931-3
3. Devi A, Jayakumar KLL (2017) Primary Synovial Sarcoma of External Auditory Canal: A Case Report. Cureus 9(7):e1498. https://doi.org/10.7759/cureus.1498
4. Specht K, Sung YS, Zhang L, Richter GH, Fletcher CD, Antonescu CR (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
5. Italiano A, Sung YS, Zhang L, Singer S, Maki RG, Coindre

JM et al (2012) High prevalence of CIC fusion with double-homeobox (DUX4) transcription factors in EWSR1-negative undifferentiated small blue round cell sarcomas. Genes Chromosomes Cancer 51(3):207–218. https://doi.org/10.1002/gcc.20945

6. Kawamura-Saito M, Yamazaki Y, Kaneko K, Kawaguchi N, Kanda H, Mukai H et al (2006) Fusion between CIC and DUX4 up-regulates PEA3 family genes in Ewing-like sarcomas with t(4;19)(q35;q13) translocation. Hum Mol Genet 15(13):2125–2137. https://doi.org/10.1093/hmg/ddl136
7. Antonescu CR, Owosho AA, Zhang L, Chen S, Deniz K, Huryn JM et al (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
8. Yoshida A, Goto K, Kodaira M, Kobayashi E, Kawamoto H, Mori T et al (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
9. Connolly EA, Bhadri VA, Wake J, Ingley KM, Lewin J, Bae S et al (2022) Systemic treatments and outcomes in CIC-rearranged Sarcoma: A national multi-centre clinicopathological series and literature review. Cancer Med 11(8):1805–1816. https://doi.org/10.1002/cam4.4580
10. Brahmi M, Gaspar N, Gantzer J, Toulmonde M, Boudou-Rouquette P, Bompas E et al (2023) Patterns of care and outcome of CIC-rearranged sarcoma patients: A

nationwide study of the French sarcoma group. Cancer Med 12(7):7801–7807. https://doi.org/10.1002/cam4.5539

11. Doll S, Schweizer L, Bollwein C, Steiger K, Pfarr N, Walker M et al (2024) Proteomic Characterization of Undifferentiated Small Round Cell Sarcomas With EWSR1 and CIC::DUX4 Translocations Reveals Diverging Tumor Biology and Distinct Diagnostic Markers. Mod Pathol 37(7):100511. https://doi.org/10.1016/j.modpat.2024.100511
12. Yoshimoto T, Tanaka M, Homme M, Yamazaki Y, Takazawa Y, Antonescu CR et al (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
13. Hung YP, Fletcher CD, Hornick JL (2016) Evaluation of ETV4 and WT1 expression in CIC-rearranged sarcomas and histologic mimics. Mod Pathol 29(11):1324–1334. https://doi.org/10.1038/modpathol.2016.140
14. Gambarotti M, Benini S, Gamberi G, Cocchi S, Palmerini E, Sbaraglia M et al (2016) CIC-DUX4 fusion-positive round-cell sarcomas of soft tissue and bone: a single-institution morphological and molecular analysis of seven cases. Histopathology 69(4):624–634. https://doi.org/10.1111/his.12985
15. Brčić I, Brodowicz T, Cerroni L, Kashofer K, Serbanescu GL, Kasseroler MT et al (2020) Undifferentiated round cell sarcomas with CIC-DUX4 gene fusion: expanding the clinical spectrum. Pathology 52(2):236–242. https://doi.org/10.1016/j.pathol.2019.09.015
16. Song MJ, Cho KJ, Kim TI, Kim W, Song JS (2022) Distinct histologic and genetic characteristics of round cell

sarcoma with CIC-DUX4 fusion and comparison with Ewing sarcoma. Pathol Res Pract 231:153779. https://doi.org/10.1016/j.prp.2022.153779

17. Le Guellec S, Velasco V, Pérot G, Watson S, Tirode F, Coindre JM (2016) ETV4 is a useful marker for the diagnosis of CIC-rearranged undifferentiated round-cell sarcomas: a study of 127 cases including mimicking lesions. Mod Pathol 29(12):1523–1531. https://doi.org/10.1038/modpathol.2016.155
18. Siegele B, Roberts J, Black JO, Rudzinski E, Vargas SO, Galambos C (2017) DUX4 Immunohistochemistry Is a Highly Sensitive and Specific Marker for CIC-DUX4 Fusion-positive Round Cell Tumor. Am J Surg Pathol 41(3):423–429. https://doi.org/10.1097/pas.0000000000000772
19. Cloutier JM, Al-Rohil RN, Patel RM, Ko JS, Linos K (2025) Ancillary Tools for the Diagnosis of CIC-Rearranged Sarcoma: A Comprehensive Review. J Cutan Pathol 52(4):324–331. https://doi.org/10.1111/cup.14792
20. Macedo RT, Baranovska-Andrigo V, Pancsa T, Klubíčková N, Rubin BP, Kilpatrick SE et al (2025) Nuclear DUX4 immunohistochemistry is a highly sensitive and specific marker for the presence of CIC::DUX4 fusion in CIC-rearranged sarcomas: a study of 48 molecularly confirmed cases. Histopathology 86(3):423–432. https://doi.org/10.1111/his.15341
21. Koo SC, Cardenas M, Stow P, Neary J, Wheeler DA, Shi Z et al (2025) Comparison of Molecular Testing Methodologies for CIC-Rearranged Sarcomas. Arch Pathol Lab Med 149(10):913–921. https://doi.org/10.5858/arpa.2024-0407-OA

22. Murphy J, Resch EE, Leland C, Meyer CF, Llosa NJ, Gross JM et al (2024) Clinical outcomes of patients with CIC-rearranged sarcoma: a single institution retrospective analysis. J Cancer Res Clin Oncol 150(3):112. https://doi.org/10.1007/s00432-024-05631-7
23. Palmerini E, Gambarotti M, Italiano A, Nathenson MJ, Ratan R, Dileo P et al (2023) A global collaboRAtive study of CIC-rearranged, BCOR::CCNB3-rearranged and other ultra-rare unclassified undifferentiated small round cell sarcomas (GRACefUl). Eur J Cancer 183:11–23. https://doi.org/10.1016/j.ejca.2023.01.003
24. Sparber-Sauer M, Corradini N, Affinita MC, Milano GM, Pierron G, Carton M et al (2023) Clinical characteristics and outcomes for children, adolescents and young adults with "CIC-fused" or "BCOR-rearranged" soft tissue sarcomas: A multi-institutional European retrospective analysis. Cancer Med 12(13):14346–14359. https://doi.org/10.1002/cam4.6113
25. Mancarella C, Carrabotta M, Toracchio L, Scotlandi K (2022) CIC-Rearranged Sarcomas: An Intriguing Entity That May Lead the Way to the Comprehension of More Common Cancers. Cancers (Basel) 14(21):5411. https://doi.org/10.3390/cancers14215411