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Commentary

Teensy and Orbed-CIC Rearranged Sarcoma

Anubha Bajaj*

Department of Histopathology, Panjab University, A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University, A.B. Diagnostics, India.

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CIC rearranged sarcoma configures as an undifferentiated, small round cell soft tissue sarcoma with capicua-double homeobox 4 (CIC-DUX4) genetic fusion. The extremely exceptional, high grade, aggressive CIC rearranged sarcoma emerges as an undifferentiated small round cell sarcoma demonstrating CIC genetic fusions, commonly a CIC-DUX4 genomic fusion.

Clinical representation, histological countenance, immunological profile, molecular characteristics and genetic signature of CIC rearranged sarcoma is diverse from Ewing sarcoma and associated tumours. However, appropriate discernment of confirmatory molecular genomic fusion of CIC gene is necessitated. The sarcoma preponderantly incriminates paediatric subjects or young adults.

CIC rearranged sarcoma predominantly manifests a round cell morphology with minor epithelioid or spindle shaped cellular component. Additionally designated as undifferentiated round cell sarcoma with CIC-DUX4 fusion, the aggressive sarcoma is composed of spherical to ovoid tumour cells displaying mild nuclear pleomorphism, elevated nucleocytoplasmic ratio, variably myxoid circumscribing stroma and immune reactivity to CD99, WT1, DUX4 or ETV4. Besides, CIC-DUX4 genetic fusion may arise from chromosomal translocation t(4;19)(q35;q13) or t(10;19)(q26;q13).

CIC rearranged sarcoma commonly incriminates young adults within 3rd decade to 4th decade, may appear within paediatric subjects and demonstrates an age range of 6 years to 81 years with mean age of disease emergence at 32 years. A mild male predilection is encountered [1,2].

CIC rearranged sarcoma commonly emerges within deep seated soft tissue of trunk or distal extremities. Additionally, neoplasm may arise within head and neck, retroperitoneum, upper extremities or pelvis. Primary neoplasms may incriminate diverse viscera as renal parenchyma, gastrointestinal tract, brain or bone [1,2].

Of obscure aetiology, occurrence of CIC-DUX4 fusion onco-protein activates transcriptional potential of CIC along with expression of ETV1/4/5 configuring as a member of E26 transformation specific (ETS) family of transcription factors. Majority of instances exemplify amplification of MYC gene. Tumour cells delineate CIC-DUX4 genetic fusion on account of frequently discerned chromosomal translocation t(4;19) or t(10;19). Few neoplasms harbour CIC genetic rearrangement with non-DUX4 partner genes as FOXOE4, LEUTX, NUTM1 and NUTM2A. Besides, trisomy within chromosome 8 is encountered [1,2].

Majority of subjects manifest with a rapidly progressive, painless or painful, solitary tumefaction confined to superficial or deep seated soft tissue. Initial disease representation may manifest clinical symptoms associated with metastatic disease [1,2].

Cytological assessment depicts hyper-cellular smears composed of singly disseminated and enlarged clusters of tumour cells. Individual neoplastic cell exhibits cytoplasmic vacuoles, elevated nucleocytoplasmic ratio, eccentric spherical to elliptical nuclei, irregular nuclear contour and miniature nucleoli. Tumour cells are enmeshed within a myxoid stroma.

Mitotic figures and focal necrosis are discernible [2,3].

Upon gross examination, an enlarged, tan or whitish tumefaction is encountered. Cut surface is fleshy with foci of necrosis, haemorrhage or cystic alterations.

Adoption of frozen section for appropriate discernment of CIC-DUX4 rearranged sarcoma upon miniature tissue fragments in the absence of precise molecular evaluation appears challenging [2,3].

Upon microscopy, a solid, frequently nodular tumefaction is encountered. Infrequently, architectural patterns as fascicular articulation of neoplastic cells and reticular pattern of tumour evolution may be exemplified.

Miniature spherical to ovoid tumour cells appear permeated with amphophilic or slightly eosinophilic cytoplasm, spherical to elliptical nuclei with variable nuclear chromatin and miniature to intermediate nucleoli [2,3].

In contrast to Ewing sarcoma and associated neoplasms, significant heterogeneity within nuclear magnitude and outline is observed.

Few tumours may display a predominant spindle shaped, epithelioid, plasmacytoid or rhabdoid cellular morphology [2,3].

Mitotic figures are commonly discerned. Majority of tumefaction exemplify geographic necrosis. Moderate nuclear pleomorphism may ensue. Around one third neoplasms delineate an encompassing myxoid stroma [2,3].

CIC rearranged sarcomas characteristically display morphological features as sheets of undifferentiated round cells and partially lobulated tumour configuration with reticular or pseudo-acinar cellular arrangement. Tumour cells delineate abundant, eosinophilic cytoplasm, mild nuclear pleomorphism, enhanced nucleocytoplasmic ratio, a minimal component of epithelioid cells or spindle shaped cells and appear enmeshed within a variably myxoid stroma [2,3].

Ultrastructural examination depicts significantly heterogeneous cell density with intensely adhered or loosely disconnected cellular zones. Tumour cells appear as polygonal to pleomorphic, are pervaded with abundant intracytoplasmic glycogen and configure miniature cytoplasmic processes with spherical, ovoid, polygonal or elongated nuclei and exceptional cellular adhesions. Neuroendocrine granules are absent [2,3].

TNM staging of soft tissue sarcoma confined to trunk or extremities [3,4].

Primary tumour

- TX: Tumour magnitude cannot be assessed
- T0: No evidence of primary tumour
- T1: Tumour magnitude ≤ 5 centimetres
- T2: Tumour magnitude > 5 centimetres and ≤ 10 centimetres
- T3: Tumour magnitude > 10 centimetres and ≤ 15 centimetres
- T4: Tumour magnitude > 15 centimetres.

Regional lymph nodes

- N0: Regional lymph node metastasis absent or undetectable
- N1: Regional lymph node metastasis present.

Distant metastasis

- M0: Distant metastasis absent
- M1: Distant metastasis present into sites such as pulmonary parenchyma.

Staging of soft tissue sarcoma of trunk and extremities [3,4]

- Stage I is subdivided into
- Stage IA: T1, N0, M0, GX or G1
- Stage IB: T2, T3 or T4, N0, M0, GX or G1
- Stage II: T1, N0, M0, G2 or G3
- Stage III is subdivided into
- Stage IIIA: T2, N0, M0, G2 or G3
- Stage IIIB: T3 or T4, N0, M0, G2 or G3
- Stage IV: Any T, N1, M0, any G OR any T, any N, M1, any G.

CIC rearranged sarcoma is immune reactive to CD99, WT1 (N terminal), WT1 (C terminal), DUX4, ETV4, ERG, FLI1, calretinin, MYC or retained INI1. NUT protein appears immune reactive in sarcomas demonstrating CIC-NUTM1 genetic fusion.

CIC rearranged sarcoma appears immune non reactive to pan-cytokeratin AE1/AE3, myogenin, desmin, CCNB3, S100 protein, NY-ESO-1 or NKX2.2 [4,5].

CIC rearranged sarcoma requires segregation from neoplasms such as undifferentiated small round cell tumours, Ewing sarcoma, BCOR-CCNB3 (Ewing-like sarcoma), malignant peripheral nerve sheath tumour, synovial sarcoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumour and various soft tissue sarcomas.

CIC rearranged sarcoma can be aptly discerned with cogent tissue sampling and morphological assessment with precise immunohistochemistry and molecular characterization.

Additionally, diagnostic manoeuvers as fluorescent *in situ* hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) can be optimally employed for tumour discernment [4,5].

Upon computerized tomography (CT), CIC rearranged sarcoma appears as an iso-dense or hypodense tumefaction with heterogeneous image enhancement, in contrast to abutting skeletal muscle.

Upon magnetic resonance imaging (MRI), CIC rearranged sarcoma manifests as an enlarged, enhancing tumefaction with significant necrosis. Majority of neoplasms exhibit perilesional oedema along with flow voids or fluid-fluid levels [4,5].

T1 weighted imaging exhibits intermediate to enhanced signal intensity.

T2 weighted imaging enunciates heterogeneous, elevated signal intensity.

Upon administration of gadolinium contrast, T1 weighted imaging exhibits heterogeneous image enhancement.

Upon positron emission computerized tomography (PET/CT), an enlarged, heterogeneous, hypermetabolic tumefaction can be encountered. Positron emission tomography exhibits avid uptake of fluorodeoxyglucose (FDG).

CIC rearranged sarcoma can be optimally treated with surgical resection of the neoplasm [4,5].

Adoption of singular neoadjuvant chemotherapy is associated with inferior survival outcomes, in contrast to surgical extermination of the neoplasm followed by adjuvant chemotherapy. However, precise chemotherapeutic agents applicable for CIC rearranged sarcoma require further evaluation [4,5].

Adjuvant radiotherapy can be adopted as a treatment strategy. An estimated 55% of neoplasms subjected to aforesaid therapeutic manoeuvers may demonstrate metastasis within a median duration of 10.5 months [4,5].

Sarcomas demonstrating CIC-DUX4 genetic fusion display significantly inferior prognostic outcome, in contrast to Ewing sarcoma. Distant metastasis preponderantly ensues within pulmonary parenchyma and may occur within significant proportion of neoplasms. Estimated 5 year overall survival occurs at ~43% [4,5].

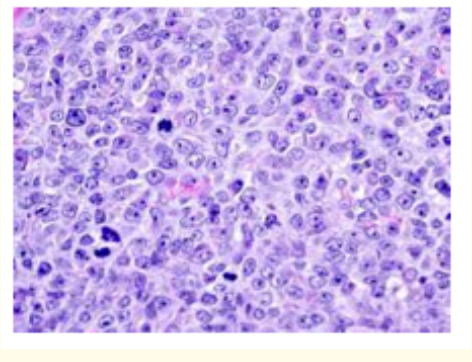

Figure 1: *CIC rearranged sarcoma delineating spherical to polygonal cells imbued with eosinophilic cytoplasm, spherical nuclei and intermediate nucleoli. Significant nuclear heterogeneity is observed [6].*

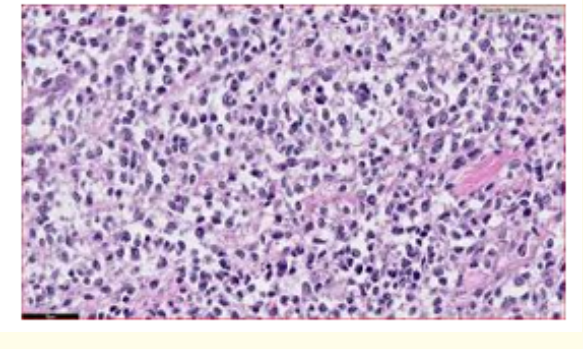

Figure 2: *CIC rearranged sarcoma demonstrating fascicles of tumour cells permeated with eosinophilic cytoplasm, spherical nuclei and miniature nucleoli. Tumour cell nuclei exhibit significant nuclear heterogeneity [7].*

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6. Image 1 Courtesy: Pathology outlines.
7. Image 2 Courtesy: American journal of case reports.

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