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Commentary

The Stringy Emend-BCOR Rearranged Sarcoma

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BCOR rearranged sarcoma is constituted of an undifferentiated round cell sarcoma characteristically displaying BCOR::CCNB3 genetic rearrangement. Previously designated as Ewing-like sarcoma, tumefaction exhibits nuclear immune reactivity to CCNB3 and BCOR along with co expression of TLE1 and SATB2 genes.

Additionally designated as BCOR::CCNB3 positive sarcoma or undifferentiated round cell sarcoma with BCOR::CCNB3 fusion, BCOR rearranged sarcoma configures ~4% of undifferentiated round cell sarcomas. BCOR rearranged sarcoma is predominantly associated with distant metastasis into pulmonary parenchyma.

BCOR rearranged sarcoma commonly arises within paediatric subjects or young adults with mean age of disease emergence at ~15 years. A male predominance is observed with male to female proportion of ~3:1.

BCOR rearranged sarcoma commonly incriminates bones followed in frequency by soft tissues and diverse viscera as renal parenchyma. Generally, tumefaction is engendered within long bones followed by pelvis and vertebral column [1,2].

Of obscure aetiology, BCOR rearranged sarcoma exhibits CCNB3 gene and BCOR::CCNB3 genetic fusion constituting as a comprehensive fusion transcript which contributes to oncogenesis and specific phenotype of the neoplasm [1,2].

An estimated 60% of BCOR genetic alterations or BCOR internal tandem duplication (ITD) and diverse partner genes as MAML3 and ZC3H7B configure the BCOR rearranged sarcoma. Paracentric inversion upon chromosome X engenders repetitive genetic fusion of BCOR which encodes BCL6 interacting corepressor situated upon chromosome Xp11.4 and CCNB3 or cyclin B3 situated upon chromosome Xp11.22 [1,2].

Genetic profiling and single nucleotide polymorphism (SNP) analysis demonstrates a distinctive cluster of neoplasms comprised of small round cell sarcomas as Ewing sarcoma [2,3].

Upon cytological examination, tumefaction is composed of spherical, spindle shaped or rhabdoid-like cells. Neoplasm is constituted of dual population of cells as an admixture of enlarged, lightly stained cells and miniature, darkly stained cells. In contrast to Ewing sarcoma or synovial sarcoma, miniature clusters of tumour cells are pervaded with thin, delicate vascular cores [2,3].

Upon gross examination, a well circumscribed, soft, fleshy, solid, homogenous, grey/white or creamy white neoplasm is encountered. Tumour magnitude varies from 5 centimetres to 15 centimetres with a median diameter of 10 centimetres. Cut surface may depict foci of necrosis. Tumour incrimination of metaphysis and diaphysis of long bones is associated with involvement of soft tissue [2,3].

Upon microscopy, neoplasm configures fascicles, sheets, nests or cords of spherical or spindle shaped cells tumour cells imbued with angulated, hyperchromatic nuclei demonstrating fine nuclear chromatin and inconspicuous nucleoli. Tumour cells may be enmeshed within a myxoid or collagenous stroma.

Neoplasm may depict miniature clusters of epithelioid cells. Foci of haemangiopericytic configuration or whorling tumour pattern may be exemplified. Focal haemorrhage or telangiectatic areas can be enunciated [2,3].

Mitotic activity is variable and ranges from 5 mitosis per 10 high power fields to 60 mitosis per 10 high power fields with a median of 30 mitosis per 10 high power fields. Miniature foci of tumour necrosis are encountered configuring 50% to 90%% of neoplastic area.

Tumefaction depicts significant variation in cellularity and histological patterns wherein an abrupt transition ensues between diverse morphological zones [2,3].

TNM staging of sarcoma of bones and joints arising within appendicular skeleton, trunk, skull and facial bones as per American Joint Committee on Cancer (AJCC) 8th edition [3,4].

Primary tumour

- TX: Primary tumour cannot be assessed.
- T0: No evidence of primary tumour.
- T1: Tumour beneath ≤ 8 centimetres in greatest dimension.
- T2: Tumour exceeding > 8 centimetres in greatest dimension.
- T3: Discontinuous tumours disseminated within incriminated primary bone.

Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed.
- N0: Regional lymph node metastasis absent.
- N1: Regional lymph node metastasis present.

Distant metastasis

- M0: Distant metastasis absent.
- M1: Distant metastasis present
    - M1a: Distant metastasis into pulmonary parenchyma.
    - M1b: Distant secondary metastasis into bone or distant sites as distant lymph node groups.
- y: Adoption of preoperative radiotherapy or chemotherapy.
- r: Stage of recurrent tumour.

Histological grade of tumours of bone and joints [3,4]:

- GX: Tumour grade cannot be assessed.
- G1: Low grade, well differentiated tumour.
- G2: High grade tumour with moderate cellular differentiation.
- G3: High grade tumour with poorly differentiated cellular component.

Staging of bone tumours arising from appendicular skeleton, trunk, skull and facial bones [3,4]:

- Stage IA: T1, N0, M0, GX or G1.
- Stage IB: T2, T3, N0, M0, GX or G1.
- Stage IIA: T1, N0, M0, G2 or G3.
- Stage IIB: T2, N0, M0, G2 or G3.
- Stage III: T3, N0, M0, G2 or G3.
- Stage IVA: Any T, N0, M1a, any G.
- Stage IVB: any T, N1, any M, any G OR any T, any N, M1b, any G.

BCOR rearranged sarcoma appears immune reactive to CCNB3, BCOR, CD99, SATB2, TLE1, Cyclin D1, BCL2 and CD56.

BCOR rearranged sarcoma appears immune non reactive to smooth muscle actin (SMA), desmin, myogenin, MyoD1, S100 protein, SOX10, NKX2.2, WT1, CD34, pan keratin (AE1/AE3), CAM5.2 or epithelial membrane antigen (EMA) [4,5].

BCOR rearranged sarcoma requires segregation from various small round cell tumours as Ewing sarcoma, CIC-DUX4 sarcoma, small cell osteosarcoma, synovial sarcoma, rhabdomyosarcoma, sclerosing epithelioid fibrosarcoma or low grade fibromyxoid tumour, malignant peripheral nerve sheath tumour or neuroblastoma [4,5].

BCOR rearranged sarcoma can be appropriately discerned with morphological evaluation of tissue samples obtained by core needle biopsy.

Additionally, diagnostic confirmation may be achieved by demonstration of BCOR::CCNB3 genetic fusion as discerned by florescent *in situ* hybridization (FISH), polymerase chain reaction (PCR) or massive parallel sequencing (MPS) [4,5].

Upon radiographic imaging, tumefaction depicts permeation of inter trabecular spaces and manifests as a lytic image or tumefaction with peripheral sclerosis. Neoplasm is invariably associated with thickening of bony cortex, a feature especially encountered within metaphysis or diaphysis of incriminated long bones [4,5].

Zone of transition is broad and periosteal reaction is significant. T1 weighted magnetic resonance imaging (MRI) delineates an isointense or hypo-intense signal intensity.

T2 weighted imaging demonstrates a heterogeneously hyper-intense signal intensity with post contrast image enhancement.

Positron emission tomography (PET/CT) enunciates a mean standard uptake value (SUV max) of ~6.3, a value which varies from 5.7 - 6.9. BCOR rearranged sarcoma can be optimally treated with therapeutic regimen akin to Ewing sarcoma [4,5].

Adoption of neoadjuvant chemotherapy with treatment strategy similar to Ewing sarcoma can be preferentially followed by surgical extermination of the neoplasm or radiation therapy, manoeuvers which are optimally adopted for localized tumour control [4,5].

Pertinent chemotherapeutic protocol for BCOR rearranged sarcoma emerges as vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide which ameliorates prognostic outcomes.

Radiotherapy is beneficially employed for treating neoplasms confined to surgically inaccessible sites, instances with unsatisfactory tumour eradication from excised tissue perimeter and as a palliative therapy. Employment of immunotherapy exhibits limited efficacy.

Prognostic outcomes appear comparable to Ewing sarcoma and are superior to the aggressive CIC-DUX4 sarcoma.

5 year overall survival appears at ~75% whereas disease free survival is ~70% [4,5].

Prognostic outcomes are contingent to appearance of regional lymph node or distant metastases. Localized disease subjected to cogent surgical resection exhibits favourable 5 year disease survival.

Neoplasms associated with distant metastasis enunciate inferior 5 year disease survival.

Surgical extermination of pulmonary metastases ameliorates individual survival [4,5].

Factors associated with favourable prognostic outcomes emerge as comprehensive pathologic response to neoadjuvant chemotherapy, miniature neoplasms confined to superficial sites and tumour confined to sites accessible to surgical extermination.

Factors associated with unfavourable prognostic outcomes appear as preliminary tumour relapse, occurrence of distant metastasis and neoplasms confined to specific anatomical sites as trunk or pelvis [4,5].

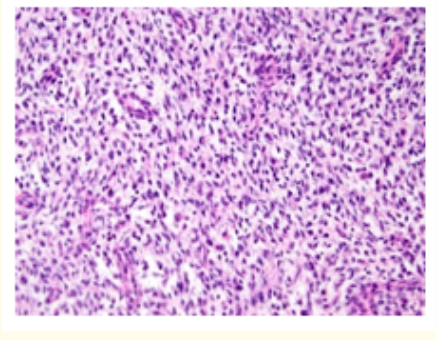

Figure 1: *BCOR rearranged sarcoma delineating nests and fascicles of spherical and spindle shaped tumour cells imbued with angulated, hyperchromatic nuclei and inconspicuous nucleoli surrounded by a mildly collagenous stroma. Few mitotic figures and focal haemorrhage is observed [6].*

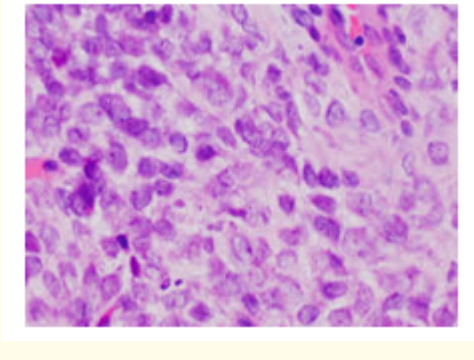

Figure 2: *BCOR rearranged sarcoma delineating bundles of spindle shaped and epithelioid cells incorporated with angulated, hyperchromatic nuclei and inconspicuous nucleoli. Surrounding stroma is myxoid [7].*

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6. Image 1: Courtesy: Pathology outlines.

7. Image 2: Courtesy: Cureus.com.

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