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Editorial

# Globate and Spheroid-Embryonal Rhabdomyosarcoma

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Embryonal rhabdomyosarcoma is a frequently discerned subtype of rhabdomyosarcoma. Tumefaction is expounded as a soft tissue neoplasm enunciating a lineage derived from undifferentiated mesoderm.

Embryonal rhabdomyosarcoma frequently emerges within adolescents or paediatric population. Anaplasia is a significant prognostic feature manifesting as prominent anisonucleosis and atypical, multipolar mitotic figures.

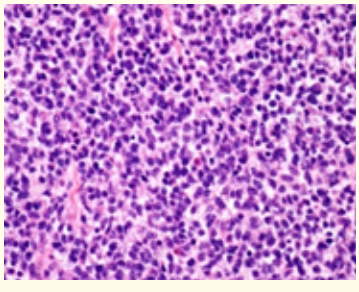

***Figure 1:*** *Embryonal rhabdomyosarcoma depicting small round cells with scanty cytoplasm, enlarged nuclei with vesicular chromatin and inconspicuous nuclei surrounded by delicate, fibro-vascular stroma [5].*

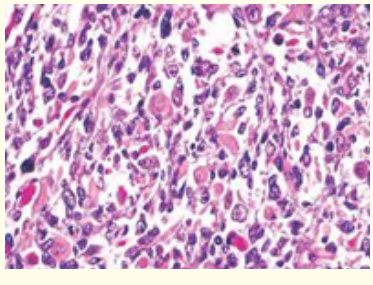

***Figure 2:*** *Embryonal carcinoma delineating small round cells commingled with anaplastic cells with abundant, eosinophilic cytoplasm demonstrating anisonucleosis, nuclear hyperplasia, hyperchromatic nuclei and skeletal muscle differentiation [6].*

Anaplastic tumour cells appear associated with chromosomal mutations within TP53 gene, overexpression of p53 protein and an inferior overall prognosis [1,2].

Tumour cell morphology is preponderantly variable with occurrence of spindle-shaped cells. Proportionate myogenic differentiation with immune reactivity to MyoD1 or myogenin is observed. Reoccurring genetic fusions are absent although recurrent copy number changes may ensue.

Diverse variants as botryoid or anaplastic varieties exhibit distinctive tumour configurations and prognostic outcomes [1,2]:

- Botryoid embryonal rhabdomyosarcoma or 'sarcoma botryoides' is confined to specific locations and appears within epithelium layered viscera or subjacent to mucosa as urinary bladder, biliary tract, vagina, upper respiratory tract, extrahepatic bile ducts or adjoining a vacant space. Eyelids or anal region may exceptionally be incriminated. Tumefaction depicts a grape-like or 'botryoid' tumour configuration.

- Spindle cell rhabdomyosarcoma composed of spindle-shaped cells was initially contemplated to be a variant embryonal rhabdomyosarcoma. Tumefaction exhibits a predilection for para-testicular soft tissue. Neoplastic cells appear as carriers of specific genetic fusions as NCOA2 and VGLL2 fusion or point mutation of MYOD1 L122R. Neoplasm is endowed with a current, provisional classification of spindled/sclerosing rhabdomyosarcoma [1,2].

Embryonal rhabdomyosarcoma is commonly discerned in children ~ 4 years although no age of tumour emergence is exempt. Though infrequent, congenital instances are documented [1,2].

Embryonal rhabdomyosarcoma is frequently discerned within head and neck, nasal cavity, oral cavity, orbit or middle ear. Besides, genitourinary tract and para-testicular soft tissues may be implicated.

Somatic soft tissues of extremities are infrequently incriminated.

Distant tumour metastasis to soft tissues, serosa, lungs, lymph nodes or bone marrow may ensue [1,2].

Embryonal rhabdomyosarcoma is derived from undifferentiated mesoderm and exhibits phenotypic or biological features of primitive skeletal muscle [1,2].

Majority of instances emerge as a sporadic tumefaction. A distinctive genetic predisposition is absent. Paediatric population depicting predisposing familial syndromes are frequently associated with defective RAS or Hedgehog pathways and an enhanced probability of emergence of embryonal rhabdomyosarcoma [1,2].

Neoplastic cells demonstrate loss of heterozygosity or loss of imprinting within chromosome 11p15.5. Chromosomal aneuploidies are frequent, especially gains of chromosome 8. Additionally, chromosomal gains are common within chromosomes 2, 11, 12, 13 and 20. However, neoplastic cells are devoid of a characteristic chromosomal translocation.

Inactivating genomic mutations of TP53 and CDKN2A and activating chromosomal mutations within RAS family of genes is encountered. Dysregulation of ALK gene or associated, significant clinical features are variably discerned [1,2].

Embryonal rhabdomyosarcoma appears as a secondary component of Costello syndrome with defective HRAS gene, neurofibromatosis type I with impaired NF1 gene, Noonan syndrome with deficient PTPN11 and associated genes, Beckwith- Wiedemann syndrome with

altered chromosome 11p15, Dicer syndrome with modified DICER1, Li-Fraumeni syndrome with defective TP53 and Gorlin syndrome with altered PTCH1 [1,2].

Chromosomal fusion of PAX/FOX01 gene is a significant feature employed for tumour staging, treatment and prognostic outcomes. Clinical grouping of embryonal rhabdomyosarcoma is contingent to extent of disease or adequacy of initial surgical intervention and is denominated as:

- Group I is comprised of paediatric population demonstrating localized rhabdomyosarcoma devoid of regional lymph node or distant metastasis. Tumefaction is comprehensively eradicated with initial surgical extermination [1,2].
- Group II is constituted of paediatric population exemplifying localized rhabdomyosarcoma with tumour cell aggregates confined to resected surgical perimeter and regional lymph node metastasis.
- Group III is composed of paediatric population demonstrating macroscopically discernible, residual tumefaction. Regional lymph node metastasis may occur whereas distant metastasis is absent.
- Group IV is constituted of paediatric population demonstrating distant tumour metastasis into viscera such as pulmonary or hepatic parenchyma, bones, bone marrow, distant skeletal muscle groups or lymph nodes [1,2].

Grossly, a greyish white, soft or firm, poorly circumscribed, infiltrative tumefaction is observed. Botryoid variant exhibits a fleshy, nodular neoplasm or polypoid projection of variable magnitude invading lumen of incriminated viscera [1,2].

Cytological examination exhibits a cellular neoplasm composed of small round cells. Intra-nuclear cytoplasmic inclusions are infrequently delineated [1,2].

Upon microscopy, tumefaction is composed of primitive mesenchymal cells demonstrating variable skeletal muscle differentiation. Typically, the moderately cellular neoplasm enunciates hypo-cellular and hyper-cellular areas commingled with a loose, myxoid stroma. Minimally cellular zones exemplify perivascular condensation of neoplastic cells.

Sheets of miniature, stellate, spindle-shaped or spherical cells incorporated with scanty or intensely eosinophilic cytoplasm, eccentric, miniature, elliptical nuclei with vesicular chromatin and inconspicuous nucleoli are observed [1,2].

Occasional tumour cells endowed with abundant, fibrillary, eosinophilic cytoplasm, designated as ‘strap cells’ with focal differentiation into rhabdomyoblasts may appear. Following chemotherapy, ‘strap cells’ appear prominent, a feature denominated as ‘chemotherapeutic induced cyto-differentiation’ [1,2].

Tumour cells with elongated cytoplasmic tails or ‘tadpole cells’ may emerge. Intensely cellular neoplasms may simulate solid variant of alveolar rhabdomyosarcoma [1,2].

Botryoid variant frequently exemplifies a ‘cambium layer’ comprised of a hyper-cellular zone subjacent to epithelial surface. Tumour cells appear undifferentiated, spherical or spindle-shaped and are incorporated with minimal cytoplasm. Mitotic activity is significant [1,2].

Characteristically, deep-seated tumefaction is minimally cellular with morphological features simulating embryonal rhabdomyosarcoma.

Exceptionally discerned variants occur as rhabdomyosarcoma with rhabdoid features or epithelioid or rhabdoid-like rhabdomyosarcoma, clear cell change exemplified in neoplastic cells or cartilaginous metaplasia appearing within diverse tumour zones [1,2].

Ultrastructural examination depicts developing fibres of striated muscle along with characteristic thick and thin filaments [1,2].

TNM staging of embryonal rhabdomyosarcoma is denominated as:

- Stage I wherein neoplasm commences in a favourable region as the orbit, bile ducts, head and neck except para-meningeal sites or genito-urinary sites except urinary bladder or prostate. Tumour magnitude is variable. Localized tumour dissemination and regional lymph node metastasis may ensue although distant metastasis is absent [2,3].

- Stage 2 exhibits a neoplasm emerging from an unfavourable site as urinary bladder, prostate, upper extremity, lower extremity or para-meningeal site as nasal passages, nasal sinuses, middle ear, nasopharynx or sites uninvolved in stage I. Tumour magnitude is ≤ 5 centimetres. Regional lymph node or distant metastasis is absent [2,3].

- Stage III wherein neoplasm commences from an unfavourable site as urinary bladder, prostate, upper extremity, lower extremity, para-meningeal site as nasal passages, nasal sinuses, middle ear, nasopharynx or sites uninvolved in stage I. Tumour magnitude is ≤ 5 centimetres with regional lymph node metastasis or tumour magnitude is > 5 centimetres with absent regional lymph node metastasis. Distant metastasis is absent [2,3].

- Stage IV wherein neoplasm of variable magnitude may commence from diverse body sites. Distant metastasis to hepatic or pulmonary parenchyma, bone, bone marrow or various body sites is observed [2,3].

Embryonal rhabdomyosarcoma is immune reactive to desmin, MyoD1, myogenin, vimentin, actin, myoglobin, myosin or creatine kinase M. Aberrant and occasional immunoreactivity to cytokeratin, S100 protein, neuro-filaments or B cell markers as CD20 may be observed. Glycogen rich tumour cells can be highlighted with Periodic acid Schiff's stain [3,4].

Botryoid variant is immune reactive to desmin, MyoD1, smooth muscle actin or muscle specific actin [3,4].

Embryonal rhabdomyosarcoma necessitates segregation from neoplasms such as alveolar rhabdomyosarcoma, desmoplastic small round cell tumour, Ewing's sarcoma or peripheral neuro-ectodermal tumour, large cell lymphoma, monophasic synovial sarcoma, myxoid liposarcoma, neuroblastoma, pleomorphic rhabdomyosarcoma, Wilm's tumour, Li-Fraumeni syndrome, lipoma, lymphadenopathy, lymphoproliferative disorders, neurofibromatosis type 1 or osteosarcoma [3,4].

Embryonal rhabdomyosarcoma is optimally treated with surgical eradication as a preferred localized therapy [3,4].

Typically, radiotherapy is employed for treating residual disease, lymph node metastasis or an inferior therapeutic response to combined chemotherapy [3,4].

Anaplastic neoplasms mandate adoption of intensive therapeutic strategies [3,4].

Botryoid variant of embryonal rhabdomyosarcoma can be subjected to conservative surgical procedures along with radiation and chemotherapy [3,4].

Prognostic outcomes are contingent to factors such as primary site of neoplasm, histologic subtype, extent of surgical manoeuvers adopted and control of localized disease [3,4].

Botryoid variant is accompanied by superior prognostic outcomes although delayed relapse may ensue [3,4].

Factors associated with favourable prognostic outcomes are age < 9 years, tumour confined to orbit or para-testicular region or absence of distant metastasis during initial surgical resection [3,4].

Emergence of focal or diffuse anaplasia exhibits an inferior prognostic outcome. Tumour incrimination of upper extremity or lower extremity is associated with frequent tumour relapse and decimated survival [3,4].

Embryonal rhabdomyosarcoma is categorized into distinct risk groups which assists adoption of pertinent therapeutic strategies and are designated as:

- Low-risk group comprised of paediatric subjects included within clinical groups I, II or III wherein neoplastic cells are devoid of PAX/FOX01 genetic fusion or paediatric population within stage II or stage III disease demonstrating clinical groups I or II and neoplastic cells devoid of PAX/FOX01 genetic fusion.
- Intermediate-risk group delineating stage II or stage III disease comprised of paediatric population included in clinical group III and neoplastic cells devoid of PAX/FOX01 genetic fusion or subjects in stage I, II or II lacking distant metastasis and neoplastic cells depicting PAX/FOX01 fusion gene or paediatric population < 10 years with disseminated, stage IV disease and neoplastic cells devoid of PAX/FOX01 genetic fusion.
- High-risk group exhibits paediatric population < 10 years with disseminated, stage IV disease and neoplastic cells devoid of PAX/FOX01 fusion gene or subjects with widespread, stage IV disease with neoplastic cells depicting PAX/FOX01 fusion gene [3,4].

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5. Image 1 Courtesy: Science photo library.

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