

Neural, Ectodermal, Mesenchymal- Ectomesenchymoma

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Received: September 29, 2020; **Published:** January 30, 2021

Preface

Ectomesenchymoma is constituted by a heterogeneous group of neoplasms engendered from the neural crest and is an exceptional, rapidly progressive, malignant neoplasm demonstrating concurrence of neuro-ectodermal and mesenchymal components. Soft tissue constituents are characterized by rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma, leiomyosarcoma, chondrosarcoma, malignant peripheral nerve sheath tumour or osseous elements. Initially scripted by Shuangshoti and Nestky in 1971, the tumefaction is additionally designated as malignant ectomesenchymoma (MEM) or gangliorhabdomyosarcoma as the neural involvement is frequently accompanied by an aggressive, malignant constituent of skeletal muscle rhabdomyosarcoma [1].

Disease characteristics

Predominantly a paediatric neoplasm, ectomesenchymoma can be discerned up to 60 years. The infrequently discerned tumefaction incriminates infants, neonates or young children beneath < 5 years. An estimated 80% neoplasms are encountered in children beneath < 15 years. Mesenchymal component represented by embryonal rhabdomyosarcoma is frequent in paediatric neoplasms. Around 20% tumours are discerned in adults [2].

A male predominance is observed with a male to female proportion of 1.5:1. However, specific racial or ethnic predilection is absent. Tumour magnitude varies from 3 centimetres to 18 centimetres with an average diameter of 5 centimetres [2,3].

The neoplasm can arise in brain or soft tissue and is frequently delineated within head and neck, orbit, nasopharynx, central nervous system, abdomen, retroperitoneum, pelvis, perineum, scrotum, external genitalia, para-testicular tissue, prostate or extremities [2,3].

The infrequent ectomesenchymoma arises from soft tissues of central nervous system, comprised of neuro-ectodermal elements such as ganglion cells and configures well differentiated or poorly differentiated neoplasia of neuroblastic cell origin as the ganglioneuroma, neuroblastoma, ganglioneuroblastoma or peripheral primitive neuroectodermal tumour (PNET), admixed with mesenchymal, neoplastic elements commonly represented by skeletal muscle induced rhabdomyosarcoma [2,3].

Neural component of ectomesenchymoma is constituted by neuroblasts and/or ganglion cells. Generally, well differentiated neuroblastic cells configure neuroblastoma, ganglioneuroblastoma, ganglioneuroma or a peripheral neuroectodermal tumour. Therefore, the neoplasm can be categorized as a peripheral nerve neoplasm or a rhabdomyosarcoma with neuronal differentiation [2,3].

Disease pathogenesis

Of obscure genesis, ectomesenchymoma commonly demonstrates genetic anomalies identical to embryonal rhabdomyosarcoma. Ectomesenchymoma is posited to arise from remnants of migratory neural crest cells which configures the ectomesenchyme with consequent

incrimination of skeletal muscle and neural elements. Tumefaction demonstrates a bi-phenotypic expression within the cellular component [3,4].

Although ectomesenchymoma is associated with genetic anomalies recapitulating chromosomal aberrations encountered in malignant embryonal rhabdomyosarcoma, the neoplasm is devoid of specific predisposing factors [3,4].

Clinical elucidation

Clinical representation pertains to localization of the neoplasm. Ectomesenchymoma is usually asymptomatic during initial tumour evolution. Rapidly progressive, infiltrative neoplasms appear upon superficial cutaneous surfaces or within deep-seated locations [4,5].

Clinical symptoms are nonspecific and generally arise secondary to localized tumour compression and infiltration into abutting soft tissue. Brisk tumour evolution is accompanied by pain and sensation of a tumefaction. Tumour mass can engender compression of neighbouring viscera with consequent obstruction of adjacent organs [4,5].

Ectomesenchymoma appears as a poorly defined, fleshy, expansive neoplasm commonly situated in the sub-epidermal layer or arises as a deep-seated tumefaction. Tumour progression is rapid, mammoth tumour magnitude is encountered and incriminated organs depict severe functional disability [4,5].

Ectomesenchymoma can demonstrate complications contingent to tumour site and tumour stage. Enlarged tumefaction can induce a functional impairment on account of obstruction or mass effect [5].

Histological elucidation

Tumefaction may manifest as a well circumscribed, rubbery, lobular, whitish, pseudo-encapsulated, retroperitoneal mass of variable magnitude, cut surface is firm and fibrillary with miniature foci of haemorrhage and necrosis [5].

Tumefaction is predominantly comprised of ectodermal derivatives as the neuroblasts or ganglion cells along with mesenchymal elements comprised of plump, elongated cells configuring interlacing fascicles. Immature, atypical ganglion cells appear as bi-nucleated or multinucleated with appearance of Nissi granules. Neurofibromatous and neuroblastic components configure rosettes [5].

On microscopy, a pleomorphic sarcoma composed of spindle-shaped cells associated with rhabdomyoblasts is denominated. Tumefaction is excessively vascular with innumerable capillaries and is associated with peritumoural infiltration of inflammatory cells. Innumerable enlarged, bizarre, pleomorphic, giant cells and ganglion-like cells with enlarged, spheroidal, vesicular nuclei and prominent nucleoli are encountered. Mitotic figures are frequent [5,6].

Skeletal muscle component is composed of spheroidal to elliptical cells incorporated with abundant glycogen-rich cytoplasm. Cross striations are characteristic. Neuronal component resembling ganglioneuroma depicts hypo-cellular areas composed of spindle-shaped cells with elongated, eosinophilic cytoplasmic processes and wavy, pointed nuclei. Normal ganglion cells are admixed within the neoplastic cellular component [5,6].

Rhabdomyoblastic, skeletal muscle differentiation with strap-like and racquet-shaped cells is commonly denominated. Myofibril-like arrangements and cellular cross striations are observed. Additionally, liposarcoma-like, chondroid foci, fibrosarcoma-like or fibrous histiocytoma-like tumour zones with multinucleated giant cells are detected [5,6].

Ectodermal component can be scarce, especially following chemotherapy. Occasionally, ganglioneuroma-like foci can be exuberant. Tumour necrosis and haemorrhage are encountered.

Ectomesenchymoma can be hyper-diploid and demonstrates translocations of chromosome 12 and chromosome 15. A subset of tumour cells display hyperploidy and gains within chromosomes 2,11 and 20. Distinctive translocations of chromosome t(6p21.32-p21.2) and genetic amplification 6p11.2 are denominated. Aforesaid genomic aberrations can disappear following chemotherapy [5,6].

Immune histochemical elucidation

Ectomesenchymoma is intensely and diffusely immune reactive to desmin, especially within rhabdomyoblasts, giant cells and spindle-shaped cells. Skeletal muscle component is immune reactive to desmin and muscle specific actin (MSA). Rhabdomyofibroblasts and miniature, poorly differentiated cells are immune reactive to desmin and myosin [2,3].

Ganglion cells and tumour giant cells are diffusely immune reactive to synaptophysin. Ganglioneuroma element and neural foci are variably immune reactive to S100 protein. Ganglion cells are intensely immune reactive to neuron specific enolase (NSE). The neoplasm is intensely immune reactive to high mobility group A1 (HMGA1) and high mobility group A2 (HMGA2) proteins, an expression which decimates following therapy, thus indicating concurrent oncogenic expansion of HMGA proteins [3,4].

The neoplasm is immune non reactive to cytokeratin [2].

Differential diagnosis

Ectomesenchymoma requires segregation from rhabdomyosarcoma, benign and malignant triton tumour, teratoma, Wilm's tumour and benign, mature ectomesenchymoma or ectomesenchymal hamartoma [7,8]:

- Rhabdomyosarcoma and diverse variants indicate malignant metamorphosis of the skeletal muscle component. Appropriate discernment of ganglion cells may be challenging on fine needle aspiration or core needle biopsy due to tumour variability at diverse sites [6,7].
- Wilm's tumour is a triphasic neoplasm with predominance of a singular component. Blastema is composed of miniature to medium, spherical cells with uniform nuclei. Epithelial component is heterologous with epithelium and glia besides configuring rosettes, tubules or papillary articulations. Stromal element is variably cellular with spindle-shaped cells and diverse mesenchymal elements as the skeletal muscle, adipose tissue or cartilage [6,7].
- Triton tumour delineates mature neural tissue intricately intermixed with mesenchymal cells and skeletal muscle fibres. The multinodular neoplasm is extensively vascular, is immune reactive to epithelial membrane antigen (EMA) and can be highlighted with Masson's trichrome or phospho-tungstic acid haematoxylin (PTAH) stain.
- Teratoma is a triphasic tumour composed of ectoderm, mesoderm and endoderm. Tumefaction may be solid or cystic. Glial tissue and cutaneous adnexal structures are commonly discerned [6,7].
- Ectomesenchymal hamartoma is a lobular malformation exemplifying garland-shaped articulations admixed with fine collagen fibres. Extracellular space is incorporated with myxoid matrix. The neoplasm is immune reactive to glial fibrillary acidic protein (GFAP) and immune non reactive to desmin, smooth muscle actin (SMA) or epithelial membrane antigen (EMA) [6,7].

Investigative assay

Ectomesenchymoma can be adequately discerned with appropriately assessed history and comprehensive physical examination. Ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI) of incriminated tumour zones can be suitably adopted [7,8].

Computerized tomography (CT) of pelvic neoplasms demonstrates anterior displacement of urinary bladder and rectal compression. Whole body positron emission computerized tomography (PET-CT) of implicated tumour zones is employed to assess tumour metastasis and appropriate tumour staging [7,8].

Competent and comprehensive tissue evaluation of the neoplasm is mandatory for definitive diagnosis and commencement of therapy. Fine needle aspiration cytology can be employed although the procedure is of limited utility as diverse tumour regions are inadequately represented or may be misinterpreted. Core needle biopsy or surgical extraction of tumour tissue is an appropriate diagnostic manoeuvre [7,8].

Neural component of ectomesenchymoma can be misinterpreted. Emergence of enlarged, spherical cells with vesicular nuclear chromatin and prominent nucleoli are indicative of a neoplasm comprised of neuro-ectodermal and mesenchymal elements [7,8].

On cytogenetic evaluation, the neoplasm recapitulates an embryonal rhabdomyosarcoma which demonstrates loss of heterozygosity or loss of imprinting at chromosome 11p15.5. Chromosomal aneuploidies are frequent. Gains of chromosome 8 is discerned in the majority (90%) of neoplasms. Additionally, genetic gains are denominated in chromosome 2, 11, 12, 13 and 20. The neoplasm is devoid of definitive chromosomal translocations. Inactivating genomic mutation of TP53 and CDKN2A and activating mutation of RAS genes is observed. Occurrence and frequency of anaplastic lymphoma kinase (ALK) genetic dysregulation is debatable [7,8].

Therapeutic options

Ectomesenchymoma can be appropriately managed with combination therapy comprised of surgical eradication, chemotherapy and radiation therapy. Comprehensive surgical extermination of the neoplasm with eradication of a broad, tumour- free perimeter of uninvolved soft tissue is recommended [7,8].

Adjuvant radiation and intensive chemotherapy can be employed following wide surgical excision. The neoplasm treated by aggressive chemotherapy and adequate surgical extermination is accompanied by a disease-free interval of approximately 7 months to 50 months [7,8].

Advanced, high grade neoplasms or tumour metastasis can be subjected to adjuvant radiation or chemotherapy. Arterial embolization of the neoplasm can be adopted to temporarily alleviate clinical symptoms and decimate surgery induced haemorrhage. Significant post-operative care with minimal activity is mandatory for appropriate wound healing. The tumour can metastasize to localized and distant regions. Localized tumour reoccurrence can appear following surgery. Surgical extermination can engender mutilation of vascular articulations, vital organs and adjacent soft tissue [7,8].

Extended monitoring, regular screening, physical examination, haematological, biochemical and radiological investigations are necessitated to appropriately evaluate localized tumour reoccurrence and distant metastasis [7,8].

Administration of chemotherapy is associated with toxicity and radiation induced, organ specific or soft tissue fibrosis. Achievement of radical surgical ablation is a significant prognostic factor [8].

Prognostic outcomes are contingent to tumour magnitude, extent of tumour infiltration, pertinent tumour stage and response to therapy. Site confined, superficial, cutaneous, low grade, primary neoplasms with absent concurrent malignancies and tumour magnitude below < 10 centimetres demonstrate superior therapeutic outcomes, in contrast to high grade, relapsing or metastatic neoplasms [7,8].

Preliminary diagnosis, prompt therapeutic intervention and favourable response to diverse treatment methodologies is associated with favourable prognosis. Enhanced proportion of cellular propagation, bulky or progressive neoplasms, incrimination of elderly individuals or vital organs, regional lymph node involvement and tumefaction unamenable to surgical resection is associated with inferior prognosis [7,8].

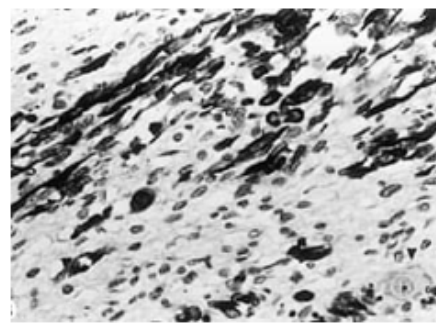


Figure 1: Ectomesenchymoma delineating accumulation of spindle-shaped cells with a commixture of ganglion cells with abundant, angulated cytoplasm and vesicular nuclei [9].

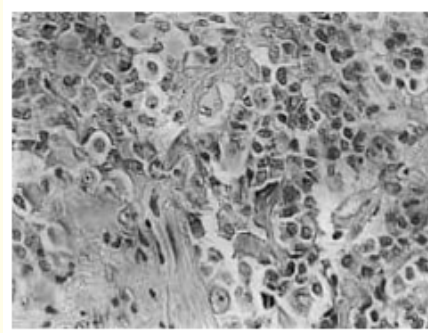


Figure 2: Ectomesenchymoma composed of intermixed spindle-shaped cells and enlarged ganglion cells with abundant, angulated cytoplasm [10].

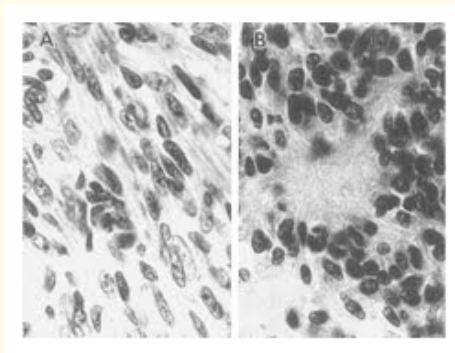


Figure 3: Ectomesenchymoma exemplifying aggregates of spindle-shaped cells with wavy nuclei admixed with enlarged ganglion cells with abundant, angulated cytoplasm and vesicular nuclei [11].

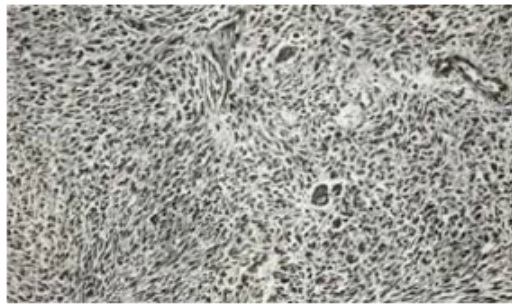


Figure 4: Ectomesenchymoma enunciating whorls of spindle-shaped, mesenchymal cells commingled with enlarged ganglion cells with abundant cytoplasm [12].

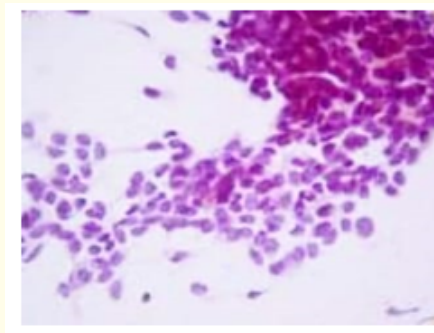


Figure 5: Ectomesenchymoma on fine needle aspiration exhibiting aggregates of spindle-shaped cells intermixed with enlarged, ganglion-like cells with abundant, angulated, eosinophilic cytoplasm [13].

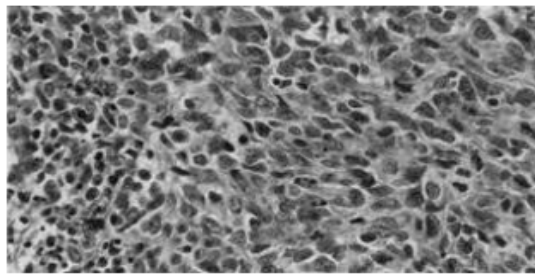


Figure 6: Ectomesenchymoma delineating an admixture of spindle-shaped mesenchymal cells admixed with enlarged ganglion cells with angulated cytoplasm [14].

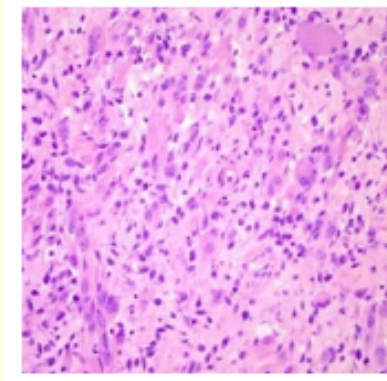


Figure 7: Ectomesenchymoma depicting an amalgamation of spindle-shaped cells admixed with mature ganglion cells with abundant, angulated cytoplasm and vesicular nuclei [15].

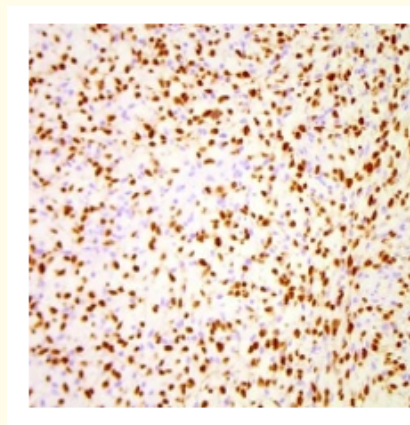


Figure 8: Ectomesenchymoma demonstrating immune reactivity to myogenin [15].

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Volume 10 Issue 2 February 2021

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