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Guest Editorial

The Sinewy Babyhood- Fibrous Hamartoma of Infancy

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Preface

Fibrous hamartoma of infancy is an exceptional, benign, paediatric, tumour-like condition. Characteristically, the superficial, poorly circumscribed, soft tissue neoplasm is composed of triphasic, organoid architecture of proportionate, mature fibroblastic tissue, mature adipose tissue and immature mesenchyme.

Fibrous hamartoma of infancy was initially scripted by Reye in 1956 as a "subdermal fibromatous tumour of infancy". Triphasic morphology comprised of bland fascicles of fibroblastic tissue, mature adipose tissue and nodules of primitive, myxoid mesenchyme possibly represents a reactive phenomenon as constituents demonstrate an orderly maturation with emergence of adult fibrous tissue [1].

Subsequently, the neoplasm was designated as "fibrous hamartoma of infancy" by Enzinger in 1965 due to clinical representation of the neoplasm in infants or young adults, absence of preceding injury and a uniform, organoid countenance of a hamartoma, instead of a reparative process [2].

Distinctive tumour components are dense, fibro-collagenous tissue, loosely articulated, immature, spheroidal, mesenchymal cells and mature adipose tissue. Cellular concentration within fibroblastic and primitive mesenchymal region is variable.

Disease characteristics

Although fibrous hamartoma of infancy is a frequent childhood mesenchymal neoplasm, it comprises of an estimated 0.02% of benign, soft tissue neoplasms.

The tumefaction is frequently delineated within anterior or posterior axillary folds, upper arm, chest wall, shoulder, axilla, scapula, thigh, inguinal region, buttocks, trunk, forearm, scrotum, external genital region, head, neck or face. Neoplasm appearing in older or middle aged individuals incriminates acral sites such as hand or foot. Around 7.5% neoplasms are detected within the cranio-cervical region [3,4].

Generally, lesion distribution is denominated as axilla (17%), trunk dorsal region (16%), upper arm (14%), scrotum (9%), chest wall (8%), thigh (6%), neck (5%), breast (4%), forearm (4%), abdominal wall (3%), buttock (3%), cheek (2%), foot (2%), shoulder (2%), finger (1%), scalp (1%), flank (1%), hip (1%) and orbit (1%) [3,4].

Tumour magnitude varies from 0.4 centimetres to 17 centimetres with a mean tumour diameter of 3 centimetres.

The neoplasm can be detected from birth to 14 years with a mean age of tumour discernment at 15 months. Majority of neoplasms manifest within first two years wherein around 91% occur within the first year. Approximately one fourth (25%) tumours are congenital. The tumefaction is infrequent following puberty [3,4].

A male predominance is observed with a male to female proportion of 2.7:1.

Although nomenclated as a hamartoma, fibrous hamartoma of infancy can be contemplated as a tumefaction as it arises as a congenital lesion and exceptionally coexists with foci of sarcomatous morphology. The neoplasm is accompanied by diverse cytogenetic alterations.

Specific instances depict pertinent cytogenetic anomalies with complex karyotype t (6;12;8) (q25;q24.3;q13) or complex structural rearrangement incriminating chromosome 1,2,4 and 17 or a reciprocal chromosomal translocation t (2;3) (q31;q21) [3,4].

Cogent genetic manifestations and possible localized tumour reoccurrence posits a neoplastic instead of engendered hamartoma emergence of the nodule.

Congenital instances of fibrous hamartoma of infancy associated with sarcoma-like transformation demonstrates a hyper-diploid or near tetraploid karyotype accompanied by copy neutral loss of heterozygosity (LOH) of chromosome 1p and chromosome 11p. Malignant appearing fibrous hamartoma of infancy depicts a decimation of chromosome 10p, chromosome 14 and a segment of chromosome 22q (22q11.23q13.33). Genomic copy number modifications, as assessed by microarray techniques, are associated with sarcoma-like morphology. Complex anomalies with hyper-diploid or near tetraploid chromosomal copy, structural alterations and copy neutral loss of heterozygosity (LOH) are discerned. Aforesaid complex karyotype is exhibited in malignant neoplasia or high grade sarcomas [3,4].

Clinical or histological occurrence of malignant fibrous hamartoma of infancy is undocumented.

Clinical elucidation

Fibrous hamartoma of infancy is solitary, rapidly progressive, painless, mobile nodule confined to subcutaneous tissue or deep-seated dermis of diverse tumour sites. Alternatively, the neoplasm can manifest as a gradually progressive, non tender mass. Multiple tumour nodules can appear upon preferred sites. Occasionally, the neoplasm is adherent to underlying fascia whereas skeletal muscle is exceptionally appended. Superimposed stratified squamous epithelium demonstrates discoloration, oedema, hypertrichosis and tethered cutaneous surface [4,5].

The tumefaction is infrequently associated with diverse, non-syndromic clinical symptoms such as multiple, discrete, synchronous lesions, hypertrichosis, hyperhidrosis, tuberous sclerosis or Williams syndrome. Calcification is exceptional and chondroid component or vascular thrombosis is absent [4,5].

Sarcoma-like foci appearing within fibrous hamartoma of infancy delineate enlarged tumefaction, rapid tumour progression, infiltrative pattern of tumour evolution or localized tumour reoccurrence. Aforesaid transformation is admixed with categorical areas of benign, triphasic fibrous hamartoma of infancy [5].

Histological elucidation

Macroscopically, poorly circumscribed, solitary, grey/white, encapsulated, variably myxoid, globular, soft tissue nodule is discerned. Variable quantities of yellowish, mature adipose tissue are intermixed with grey to tan fibrous tissue. Majority of lesions are beneath < 5 centimetres in magnitude. Exceptionally, tumour diameter exceeding > 10 centimetres is denominated. Cut surface is homogenous and grey/white [5,6].

On fine needle aspiration cytology, the tumefaction is moderately cellular and delineates fragments of mature adipose tissue and clusters of fibroblastic cells enmeshed within a myxoid or collagenous matrix. Mitotic activity and cellular atypia is absent [4].

On microscopy, fibrous hamartoma of infancy characteristically enunciates three distinct components configuring organoid structures. Well defined, intersecting trabeculae of fibroblastic and myofibroblastic origin with dense, fibro-collagenous tissue, composed of spindle-shaped cells with bland, straight or wavy nuclei are exhibited. Tumour cells are subdivided by varying quantities of collagen. Islands of immature, miniature, spheroidal or stellate, primitive mesenchymal cells with scant cytoplasm are intermixed within fibrous trabeculae [5,6].

Tumefaction partially displays a triphasic morphology exhibiting haphazard, intersecting fascicles of uniform fibroblastic or myo- fibroblastic cells, mature adipose tissue and prominently vascular, myxoid nodules of primitive, spindle-shaped to stellate mesenchymal cells [5,6].

The inadequately circumscribed neoplasm with predominant, organoid configuration is composed of three distinct elements defined by trabecular or stellate, immature mesenchymal cells depicting scanty cytoplasm and bland, straight or wavy nuclei wherein mesenchymal cells are enmeshed within a myxoid matrix. Fibro-collagenous tissue is constituted by uniform fibroblasts or myo-fibroblasts and are intermingled with mature adipose tissue cells. Superimposed epidermis demonstrates eccrine alterations such as epithelial hyperplasia, ductal dilatation, intraluminal papillary articulations or squamous syringo-metaplasia [5,6].

Percentage of mature adipose tissue, fibroblastic fascicles and primitive mesenchyme is variable although an even tissue distribution is observed in approximately 34% subjects wherein nearly 33% instances delineate predominance of fibroblastic tissue with roughly 33% neoplasms composed preponderantly of mature adipose tissue. Predominance of a specific morphological component is denominated by an excess > of 45% of precise neoplastic configuration [5,6].

Occasional tumours depict a preponderance of myxoid elements. Mitosis is infrequent and tumour necrosis is absent.

Around 30% neoplasms exhibit extensive zones of hyalinised tissue configuring broad, dense, collagen fascicles with pseudo-angiomatous, slit- like spaces layered by CD34 immune reactive, flattened or prominent fibroblastic cells, akin to giant cell fibroblastoma [6].

Tumour parenchyma is enmeshed within a myxoid matrix incorporated with abundant, hyaluronidase- sensitive, acid muco-polysaccharides. Primitive myxoid appearing foci frequently circumscribe miniature veins. Mature adipose tissue component is interspersed amongst spindle-shaped and primitive, spheroidal, mesenchymal cell components with fibro-collagenous tissue. Aggregates of chronic inflammatory cells are frequent [5,6].

Organoid architecture is usually preserved along with occurrence of typical, fibroblastic, adipocytic and primitive mesenchymal tissue. Several tumour nodules are composed of primitive, spheroidal mesenchymal cells with enhanced nuclear grade and mitotic activity. Production of uncommon, osteoid- like, densely eosinophilic tumour matrix is exemplified [5,6].

Keratinized, stratified squamous epithelial lining envelops a neoplasm composed of mature adipocytes with intersecting fascicles of fibroblastic, spindle-shaped cells and collagenous foci. Predominant pseudo-angiomatous pattern commingled with occasional foci of immature, mesenchymal tissue are discerned. The tumour is devoid of cellular or nuclear atypia [5,6].

Sarcoma-like metamorphosis of fibrous hamartoma of infancy denominates an abrupt transformation from triphasic zones to undifferentiated, spindle-shaped or spheroidal cells. Sarcoma-like metamorphosis is associated with enhanced cellularity, elevated nuclear grade and significant mitotic activity exceeding > 10 mitosis per10 high power fields [5,6].

On cytogenetic analysis, EGFR exon 20 insertion/ duplication and chromosomal mutation is characteristic. Complex translocations such as t (2;3) are infrequent [4,6].

On ultrastructural examination, fibrous trabeculae are composed of fibroblasts and myofibroblasts. Also, primitive mesenchymal cells depict slender cytoplasmic processes and are incorporated with few organelles [6].

Immune histochemical elucidation

Mature adipose tissue is immune reactive to S100 protein. Mature fibroblastic tissue is immune reactive to vimentin and smooth muscle actin (SMA). Spindle-shaped cells confined to fibrous trabeculae are immune reactive to actin and desmin. Around 53% of neoplasms or pseudo-angiomatous foci are variably immune reactive to CD34 [3,4].

Approximately 75% tumours are variably immune reactive to smooth muscle actin (SMA) within fibroblastic or myofibroblastic zones and occasionally within primitive mesenchyme. Mesenchymal component, especially giant cell fibroblastoma-like areas are immune reactive to CD34 [3,4].

The neoplasm is immune non reactive to desmin, aberrant nuclear β-catenin, keratin, epithelial membrane antigen (EMA) and ALK-1 protein. Immature mesenchymal tissue is immune non reactive to smooth muscle actin (SMA) [3,4].

Differential diagnosis

Fibrous hamartoma of infancy necessitates a segregation from adjunctive fibroblastic, myofibroblastic or adipocytic neoplasia. Adipose tissue neoplasms can be discerned by pertinent features such as age of disease onset, site of tumour incrimination and cogent radiological findings. With preponderance of a singular morphological component, fibrous hamartoma of infancy is misinterpreted as a lipoma or fibroma or fibro-lipoma or a neuroma. Neoplasms with predominant undifferentiated, mesenchymal tissue are misinterpreted as malignant tumours [7].

Infantile fibromatosis is an invasive condition arising within deep-seated tissues such as striated muscle. Differentiated fibroblasts are diffusely infiltrated and admixed with associated cells and fibres of striated muscles [7].

Pseudo-angiomatous variant of fibrous hamartoma of infancy mandates demarcation from clinically and morphologically similar giant cell fibroblastoma. Fibrous hamartoma of infancy with predominance of primitive mesenchymal component or prominent hyalinization can be misinterpreted as a giant cell fibroblastoma [7,8].

Predominant pseudo-angiomatous tumour pattern associated with disorderly fibrosis also requires distinction from adjunctive soft tissue tumours such as haemangioma, neurofibroma, schwannoma, Gardner's fibroma, giant cell fibroblastoma and solitary fibrous tumour [7,8].

Giant cell fibroblastoma or dermatofibrosarcoma protuberans delineate genetic rearrangements or amplification of platelet derived growth factor receptor β (PDGFRB), as discerned by fluorescent *in situ* hybridization (FISH) technique. In contrast, fibrous hamartoma of infancy is devoid of giant cells. Also, characteristic genetic mutations of platelet derived growth factor receptor β (PDGFRB) are absent [7,8].

Segregation of fibrous hamartoma of infancy from diverse neoplasms is contingent to proportion of mature adipose tissue, mature fibrous tissue and primitive mesenchymal elements.

Neoplasms with predominance of mature adipose tissue necessitate separation from lipofibromatosis, lipofibromatosis-like neural tumour and maturing lipoblastoma:

- Lipofibromatosis incriminates distal extremities and is comprised of an admixture of infiltrating mature adipose tissue, lipoblast- like cells and abridged fascicles of bland, fibroblastic cells [7,8].
- Lipoblastomatosis- like neural tumour characteristically occurs within superficial soft tissues of toddlers and infants. The neoplasm depicts an infiltrative pattern of tumour growth, variable cytological atypia, immune reactivity to S100 protein and CD34 along with genomic rearrangements of NTRK1 gene [7,8].
- Lipoblastoma is a well circumscribed neoplasm with distinctly lobular tumour evolution. Typically, the neoplasm contains miniature myxoid foci admixed with an abundant capillary network and scattered lipoblasts. Chromosomal rearrangements of PLAG gene are denominated [7,8].

Fibrous hamartoma of infancy with a preponderance of fibroblastic tissue requires a distinction from:

- Desmoid-type fibromatosis which is a neoplasm exceptionally detected in infants or young children. Tumefaction is denominated by compact, actively proliferating bland, myofibroblastic cells configuring elongated, sweeping fascicles which envelop thin- walled, distended vascular articulations. Desmoid- type fibromatosis depicts significant aberrant nuclear accumulation of β-catenin and genomic mutation of CTNNB1 gene [7,8].
- Myofibroma exhibits a distinctive, biphasic pattern of tumour progression with peripheral zones of hyalinised and myoid- appearing spindle-shaped cells and cellular foci of primitive cells. Occasionally, foci of centric necrosis and/or calcification are exemplified. Myofibroma exhibits a prominent, haemangiopericytoma-like vascular pattern and an absence of mature adipose tissue [7,8].
- Calcifying aponeurotic fibroma is a neoplasm denominating distinctive, calcified foci. The chondroid-appearing nodule is circumscribed by epithelioid cells, is frequently associated with osteoclast- like giant cells and delineates infiltrative fascicles of fibroblastic cells. Calcifying aponeurotic fibroma is a lesion predominantly discerned upon hand or feet. The neoplasm displays significant calcification and an absence of primitive cells intermingled within a myxoid stroma. Calcifying aponeurotic fibroma displays a characteristic FN1-EGF fusion gene.

Fibrous hamartoma of infancy with exceptional, sarcoma-like areas requires demarcation from adjunctive paediatric sarcomas such as

- Infantile fibrosarcoma wherein ancillary evaluation of characteristic ETV6 genomic rearrangements is beneficial and obtained by fluorescent *in situ* hybridization (FISH) technique [7,8].
- Spindle cell rhabdomyosarcoma wherein immune reactivity to desmin, myogenin and MyoD1 is denominated by neoplastic spindle-shaped cells [8].

Investigative assay

On radiography, a discrete soft tissue mass is discerned. Computerized tomography (CT) and magnetic resonance imaging (MRI) delineates an elliptical, spheroidal or flattened soft tissue nodule or irregular, shallow lobules [3].

Proportion of mature adipose tissue and skeletal muscle tissue subdivide the lesions into balanced and non-balanced categories. Balanced lesions depict dual equivalent, discrete components. Non-balanced lesions display a singular, predominant component. The

neoplasm preponderantly demonstrates intensity of fibrous tissue traversed with mature adipose tissue or represents a converse intensity. Traversing adipose tissue or fibrous tissue strands manifest a parallel or whirling appearance. Also, mature adipose tissue or fibrous tissue may emerge as focal aggregates within the lesion [3,4].

Tumefaction appears as well defined or ill defined, is underlying skeletal muscle or is confined to the subcutaneous layer. Nevertheless, concurrence between categories of fibrous hamatoma of infancy with tumour perimeter and extension of lesion is absent [3,4].

Upon magnetic resonance imaging (MRI), fibrous hamartoma of infancy demonstrates a signal intensity akin to lipoma or fibromatosis. Vascular articulations are discerned upon MRI. Whirling, lobular appearance is delineated upon T2 weighted imaging [3,4].

MRI demonstrates an organized configuration of adipose tissue interspersed with heterogeneous fascicles of soft tissue which indicates a fibrous hamartoma of infancy, in concurrence with appropriate clinical manifestations [4].

Fibrous hamartoma of infancy with a predominant fibrous tissue component is accompanied by minimal signal intensity upon MRI due to collagenous component and eliminates neoplasms such as infantile fibromatosis, myofibromatosis and congenital fibrosarcoma. Occasionally, demarcation from adipose tissue tumours singularly with cogent imaging characteristics can be challenging [3,4]:

- Lipoma is a common, benign neoplasm where mature adipose tissue is predominant. Tumefaction is devoid of signals from fibrous tissue strands and dilated vascular articulations [4].
- Lipo-fibromatosis is an exceptional, fibro-fatty tumour arising in infancy and childhood. Typically, the neoplasm is discerned within superficial soft tissue of distal extremities. On MRI, the neoplasm demonstrates a signal intensity concordant with mature adipose tissue interspersed with strands of fibrous tissue of low signal intensity [3,4].
- Lipoblastoma is preponderantly composed of mature adipose tissue which delineates a heterogeneous signal intensity, akin to fibrous hamartoma of infancy [4].

Nevertheless, characteristic parallel or whirling magnetic resonance appearance of fibrous hamartoma of infancy aids distinction from lipoblastoma and lipo-fibromatosis.

Additionally, genomic rearrangement for platelet derived growth factor receptor β (PDGFRB), detected by fluorescent *in situ* hybridization (FISH) technique is absent in aforesaid adipocytic neoplasms [4].

Therapeutic options

Fibrous hamartoma of infancy is usually alleviated by comprehensive or localized surgical extermination. Although newly- configured tumours are inadequately defined, neoplasms of extended duration demonstrate pseudo-encapsulation and are amenable to surgical eradication. Majority of neoplasms are alleviated by simple surgical excision, as aggressive surgical extermination is unwarranted in the essentially benign, non-reoccurring neoplasm [7,8].

Neoplasms denominating foci of undifferentiated sarcoma-like zones can be treated with chemotherapeutic agents such as vincristine, actinomycin or cyclophosphamide. Following chemotherapy, the tumefaction can be subjected to radical tumour resection [8].

Prognostic outcomes are favourable. Localized tumour reoccurrence is denominated in around 15% instances although repetitive reoccurrence is exceptional. Tumour reoccurrence can be managed with adequate surgical eradication. Proportionate localized tumour reoccurrence declines with accomplishment of tumour-free surgical perimeter [7,8].

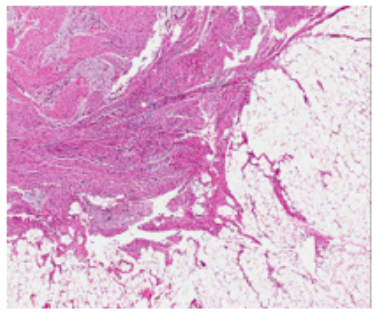

Figure 1: *Fibrous hamartoma of infancy with triphasic component of mature adipose tissue, fibroblastic tissue and primitive, spherical mesenchymal cells [9].*

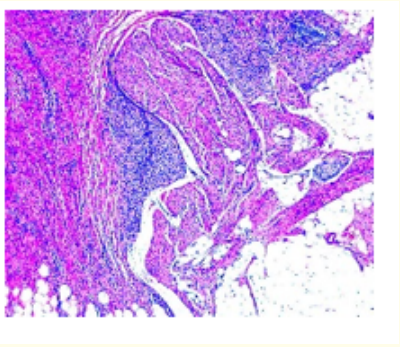

Figure 2: *Fibrous hamartoma of infancy exemplifying mature fibroblastic tissue, mature adipose tissue, immature mesenchyme and collagenous stroma [10].*

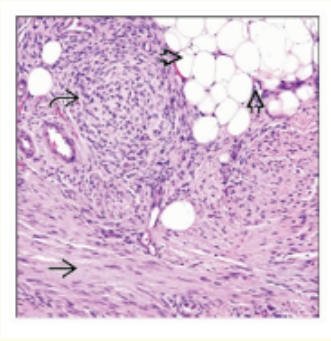

Figure 3: *Fibrous hamartoma of infancy enunciating aggregates of mature adipose tissue cells, plump fibroblastic cells and immature, spheroidal mesenchymal cells [11].*

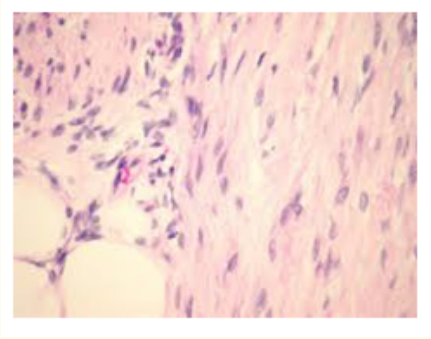

Figure 4: *Fibrous hamartoma of infancy exhibiting fascicles of fibroblastic cells, mature adipose tissue cells and immature mesenchymal cells [12].*

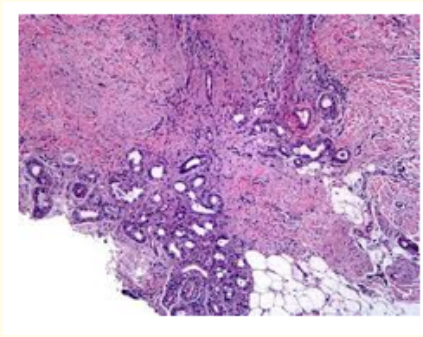

Figure 5: *Fibrous hamartoma of infancy delineating mature adipose tissue cells, abundant fibroblasts and primitive, spherical mesenchymal cells [13].*

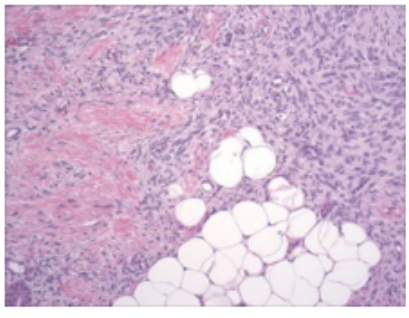

Figure 6: *Fibrous hamartoma of infancy depicting mature adipocytes, spindle-shaped fibroblasts and primitive mesenchymal cells [14].*

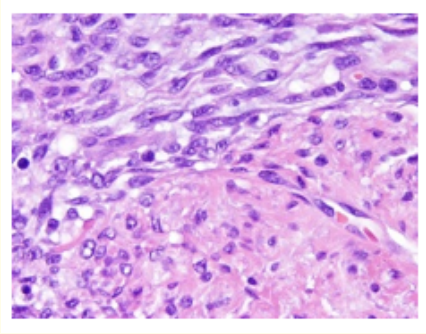

Figure 7: *Fibrous hamartoma of infancy delineating mature fibroblasts and primitive, spherical mesenchymal cells [15].*

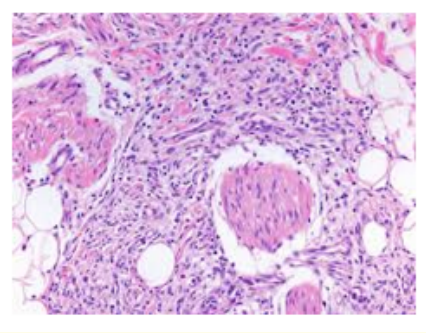

Figure 8: *Fibrous hamartoma of infancy demonstrating a triad of fibroblasts, adipocytes and primitive mesenchymal cells [16].*

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9. Image 1 Courtesy: Paediatric Orthopaedic Pathology.

10. Image 2 Courtesy: Pathology outlines.

11. Image 3 Courtesy: Basic Medical Key.

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