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# The Agglomerated Helix- Plexiform Fibrohistiocytic Tumour

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**Commentary**

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## Preface

Plexiform fibrohistiocytic tumour (PFHT) was initially scripted by Enzinger and Zhang in 1988 as a mesenchymal soft tissue neoplasm confined to subcutaneous adipose tissue and dermis. Plexiform fibrohistiocytic tumour is categorized as a fibro-histiocytic tumour of intermediate malignant potential with exceptional emergence of distant metastasis [1].

Therefore, plexiform fibrohistiocytic tumour is designated as a dermal or subcutaneous, plexiform or multinodular proliferation of fibro-histiocytic cells intermingled with osteoclast-like giant cells and chronic inflammatory cells. The neoplasm is additionally nomenclated as "plexiform fibrous histiocytoma [1,2].

## Disease Characteristics

The neoplasm is predominantly encountered in adolescents and young adults and appears within 3 years to 41 years with a mean age of tumour discernment at 15.9 years. Approximately 70% neoplasms are enunciated in individuals below< 20 years. A female predominance is observed wherein an estimated 80% of incriminated subjects are females [2]. The tumefaction is usually discerned within upper extremities or head and neck. Proximal and distal extremities are implicated in nearly 91% subjects. Plexiform fibrohistiocytic tumour is confined to the upper extremity (65%), lower extremity (27%), subcutaneous abdominal wall (13%) and head and neck (10%). Tumefaction can arise in individuals exposed to irradiation [2,3]. The neoplasm exhibits paraneoplastic syndrome with consequent, hypo-phosphatemia. Concurrence between histological features and biological behaviour is absent. The neoplasm is persistently diploid and reoccurring cytogenetic anomalies are unknown. Clonal genetic aberrations are inconsistent. Complex karyotype with numerous chromosomal deletions are observed along with a simpler karyotype 46XY t (4;15) (q21;q15) and 46Xdel(X)(q13.3)/46XX.23 [2,3].

## Clinical Elucidation

Plexiform fibrohistiocytic tumour manifests as a miniature, solitary, soft tissue nodule or flattened, firm, indurated plaque confined to subcutaneous adipose tissue. Alternatively, a painless, asymptomatic, gradually progressive, hard, dermal or subcutaneous swelling, adherent to adjacent soft tissues is discerned [3]. Plexiform fibrohistiocytic tumour commonly arises within the dermal-subcutaneous junction. Nevertheless, superficial or deep-seated or intra-dermal neoplasms are also denominated. A poorly defined, infiltrative growth is confined to dermis or subcutaneous adipose tissue although expansion into abutting skeletal muscle is infrequent [3,4].

## Histological Elucidation

On gross examination, an ill- defined, brownish nodule with several, slender, firm, grey/ white fascicles extending to the tumour perimeter is discerned. Superimposed epidermal layer is unremarkable. The firm, multinodular, poorly circumscribed neoplasm is confined to dermal or subcutaneous adipose tissue with a magnitude of beneath < 3 centimetres [3,4].

On fine needle aspiration cytology, disseminated, plump, histiocyte-like cells configure loosely cohesive sheets with vaguely defined whorls and cellular clusters. Spindle-shaped cells with elliptical nuclei and elongated, tapering cytoplasmic processes are dispersed singly and adhere to cellular aggregates. Fine nuclear chromatin demonstrates occasional, miniature nucleoli. Cellular clusters are admixed with fibro-collagenous matrix. Osteoclast-like, multinucleated giant cells are observed. Neoplastic cells lack significant nuclear pleomorphism or mitotic activity. Tumour

necrosis is absent [3,4].

The variably cellular neoplasm is composed of an admixture of fibro-histiocytic and fibroblastic cells with multinucleated giant cells intermingled within a finely granular, myxoid matrix. Singular fibroblastic cells are discerned. Osteoclast-like multinucleated giant cells may configure miniature clusters [3,4]. Hyper-cellular smears depict enlarged, branching, sheets or fragments of fibroblastic or fibro-histiocytic cells demonstrating a vaguely whorled architecture.

The neoplasm is predominantly composed of dual cell types
a) histiocyte-like cells incorporated with spherical, vesicular nuclei and ample, pale-staining cytoplasm
b) fibroblastic, spindle-shaped cells with elongated, tapering cytoplasmic processes [3,5]. On microscopy, deep-seated, dermal or subcutaneous neoplasm configuring radiating tumour extensions into adjacent skeletal muscle or adipose tissue is discerned. Plexiform or multinodular proliferation of fibro-histiocytic cells with minimal atypia is exemplified. Intermingled osteoclast –like, multinucleated giant cells and chronic inflammatory cells are denominated [5].

Nodules and cellular aggregates configure a characteristic, plexiform tumour architecture. Vascular articulations are prominent, sclerotic and dilated. Focal haemorrhage and hemosiderin pigment deposits are frequently discerned. Superimposed dermis and epidermal layer are unremarkable. Tumour invasion of vascular articulations are discerned in around 10% to 20% neoplasms [5]. Three distinct, benign morphological patterns are discerned, denominated as fibroblastic, fibro-histiocytic and mixed configuration with an exceptional, myxoid variant, composed of distinctive, variably quantifiable cellular subtypes as spindle-shaped, fibroblast- like cells, mononuclear histiocyte- like cells and multinucleated, osteoclast- like giant cells [4,5].

Around 43% tumefaction display fibro-histiocytic cellular configuration wherein tumour nodules articulate spherical or spindle-shaped cells with disseminated, osteoclast-like, multinucleated giant cells. Chronic inflammatory cells, focal micro-haemorrhages and hemosiderin pigment deposits are observed. Nearly 23% tumours are fibroblastic and are intermixed with plexiform fascicles comprised of uniform, spindle-shaped cells. Approximately 34% neoplasms exemplify a mixed tumour articulation constituted by aforesaid cellular categories [3,5].

The tumefaction is composed of elliptical to epithelioid cells configuring cellular nests, spheroids, nodules or sheets subdivided by collagenous stroma. Neoplastic cells simulate histiocyte-like cells with pale, eosinophilic cytoplasm, spherical nuclei, open nuclear chromatin and inconspicuous nucleoli. Varying quantities of osteoclast-like, multinucleated giant cells are discerned [4,5].

The nodular, subcutaneous neoplasm depicts a plexiform cellular arrangement separated by dense fibro-collagenous stroma. Infiltrative, multifocal fascicles of radiating, tongue-like, fibroblastic tissue extend into tumour periphery and focally infiltrate adjacent skeletal muscle. Irradiating, tongue- like extensions arising from neoplastic epicentre are associated with scattered, miniature, plexiform nodules constituted by histiocytic cells. Tongue- like, expansive bands are variably cellular and are composed of fibroblastic or fibromatosis- like zones [4,5].

Numerous osteoclast- like, multinucleated giant cells are intermingled within the cellular areas. Typically, significant cytological atypia, hyperchromatic nuclei, enhanced or atypical mitotic activity or foci of tumour necrosis is absent [5]. Occasional pleomorphic cells are observed. Mitotic figures are discerned up to 7 mitosis per 10 high power fields. Additionally, myxoid alterations, bony articulations and foci of cytological atypia are exceptional features. Fibrous tissue eventually substitutes the cellular nodules in ancient lesions [4,5]. On ultrastructural examination, tumour cells are comprised of an admixture of fibroblasts, myofibroblasts and undifferentiated mesenchymal cells [2,4].

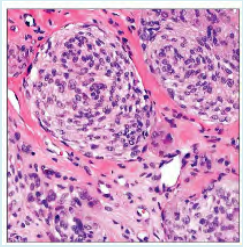

**Figure 1:** Plexiform fibrohistiocytic tumour constituted of nodules histiocyte-like cells, giant cells, fibroblastic cells, fibro-histiocytic cells, enmeshed within a fibro-collagenous stroma [9].

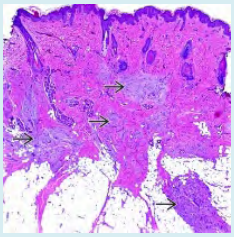

**Figure 2:** Plexiform fibrohistiocytic tumour delineating aggregates of histiocytoid cells, fibroblastic and fibro-histiocytic cells with an enveloping collagenous stroma and a superimposed epidermal layer [9].

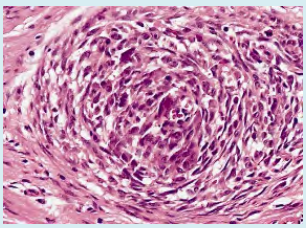

**Figure 3:** Plexiform fibrohistiocytic tumour depicting nodules of histiocytoid cells, few giant cells, fibroblastic and fibro-histiocytic cells intermixed within a fibrotic stroma [10].

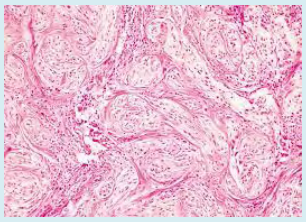

**Figure 4:** Plexiform fibrohistiocytic tumour exhibiting nodules of histiocyte-like cells, multinucleated giant cells, fibroblastic and fibro-histiocytic cells circumscribed with collagenous stroma [11].

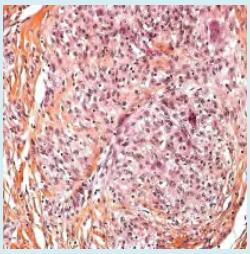

**Figure 5:** Plexiform fibrohistiocytic tumour delineating nodules of histiocytoid cells admixed with fibro-histiocytic and fibroblastic cells enmeshed within a collagenous stroma [12].

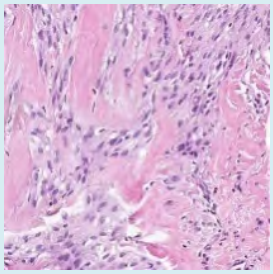

**Figure 6:** Plexiform fibrohistiocytic tumour displaying nodules of histiocytoid cells intermingled with fibroblastic and fibrohistiocytic cells with intermingled collagenous stroma [13].

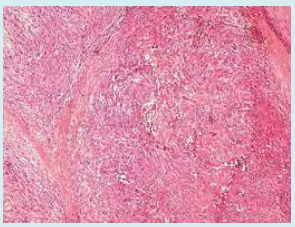

**Figure 7:** Plexiform fibrohistiocytic tumour composed of nodular, histiocyte-like cellular aggregates, giant cells, fibroblastic and fibro-histiocytic cells and an encompassing collagenous stroma [14].

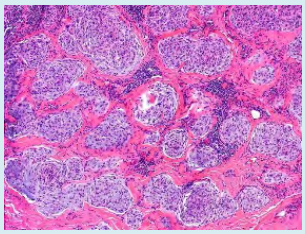

**Figure 8:** Plexiform fibrohistiocytic tumour composed of nodules of histiocytoid cells, few multinucleated giant cells and fibroblastic cells with a fibrotic stroma [15].

## Immune Histochemical Elucidation

Myofibroblastic spindle-shaped cells and histiocyte-like cells are diffusely immune reactive to smooth muscle actin (SMA), focally immune reactive to CD163 and occasionally immune reactive to calponin. Histiocyte-like cells, spherical tumour cells and multinucleated, non- neoplastic giant cells are intensely immune reactive to CD68 and vimentin. The neoplasm is diffusely immune reactive to histiocytic markers such as NKI-C3 or CD68 and occasionally immune reactive to alpha-1-antitrypsin and alpha-1-antichymotrypsin [2,4].

The neoplasm is immune non-reactive to epithelial membrane antigen (EMA), h-caldesmon, factor XIIIa (FXIIIa), factor VIII or CD34. Tumour cells are immune non-reactive to cytokeratin (AE1/AE3, CAM5.2), human melanoma black 45(HMB-45) antigen, SOX10, S100 protein, desmin, CD31, CD21, ERG, CD23, CD45, CD35 and human herpes virus 8 (HHV8) [2,4].

## Differential Diagnosis

Cytological smears comprised of cellular sheets of spindle-shaped cells with an absence of significant nuclear pleomorphism require segregation from dermatofibrosarcoma protuberans, low grade leiomyosarcoma or malignant peripheral nerve sheath tumour.

- Dermatofibrosarcoma protuberans demonstrates tumour cells configuring a storiform pattern
- Leiomyosarcoma delineates neoplastic cells articulating fascicles
- Fibroma variant of epithelioid sarcoma and monophasic, spindle cell synovial sarcoma are exceptional neoplasms which are immune reactive to cytokeratin and epithelial membrane antigen (EMA) [6,7].
- Plexiform variant of neurofibroma and schwannoma are benign mesenchymal neoplasms which can exhibit a plexiform pattern of tumour evolution. However, absence of Verocay bodies and immune non-reactive S100 protein eliminate a peripheral nerve sheath tumour. Generally, neurofibroma demonstrates an absence of plexiform nodules composed of histiocyte-like cells and is immune reactive to S100 protein [6,7].
- Plexiform fibrohistiocytic tumour can exhibit a predominantly fibroblastic tumour configuration with inconspicuous histiocyte-like cellular component, simulating diverse fibromatosis-like lesions. Fibromatosis generally displays a diffuse tumour infiltration, is predominantly centred upon skeletal muscle and is accompanied by an absence of nodular or plexiform cellular aggregates of histiocyte-like cells. Deep-seated fibromatosis is immune reactive to nuclear β-catenin [6,7].
- •Benign fibrous histiocytoma is a neoplasm appearing in elderly population and demonstrates a prominent population of foamy macrophages. Plexiform extensions of fibrous tissue, nodules comprised of histiocyte-like cells and osteoclast-like, multinucleated giant cells are usually absent [6,7].
- Fibrous hamartoma of infancy is comprised of immature cells intermingled within a myxoid stroma.
- giant cell tumour of soft tissue is constituted by infiltrative nodules composed of an admixture of multinucleated giant cells and spindle-shaped cells. Mitotic figures are frequent.
- Spindle cell melanoma, spindle cell carcinoma, follicular dendritic cell sarcoma and Kaposi's sarcoma are neoplasms with significant nuclear atypia [6,7].
- Absence of epidermal incrimination and immune non reactivity to human melanoma black 45(HMB-45) antigen, SOX10 or S100 protein essentially eliminate spindle cell melanoma [6,7].
- Immune non-reactive cytokeratin and endothelial markers CD31, ERG and absence of human herpes virus 8 (HHV8) exclude spindle cell carcinoma and Kaposi's sarcoma [6,7].
- Nodular tumour architecture configured of mononuclear, histiocyte-like cells admixed with giant cells may indicate a granulomatous inflammatory process. However, osteoclast-like, multinucleated giant cells are discerned, instead of Langerhans type of giant cells. Also, centric caseous necrosis is absent in histiocytic and giant cell-rich nodules of plexiform fibrohistiocytic tumour [5,7].
- Nodular fasciitis is a miniature, rapidly enlarging neoplasm which is devoid of hyperchromatic nuclei, cellular pleomorphism and atypical mitotic figures. The cellular tumefaction is encompassed within a loose, immature stroma [2,4].
- Cellular neurothekeoma (CNT) is a poorly marginated, lobulated, micro-nodular neoplasm composed of histiocyte-like cells, infiltrating the subcutaneous adipose tissue. Cellular neurothekeoma is composed of diverse cellular elements and depicts a uniform population of epithelioid cells. Distinctive nodules of histiocyte-like cells or osteoclast-like, multinucleated giant cells are absent. Cytological atypia and mitotic activity are enhanced. Although immune reactive to podoplanin, the neoplasm is intensely, diffusely immune reactive to microphthalmia transcription factor (MiTF). In contrast, plexiform fibrohistiocytic tumour, especially the fibrohistiocytic variant, is a well-defined, nodular neoplasm with significant plexiform articulation [2,4].

## Investigative Assay

Preoperative imaging demonstrates a tumour plaque, singular, solid nodule or an infiltrative tumefaction. The subcutaneous tumefaction abuts bone, tendon or nerve, extends to cutaneous surfaces or infiltrates skeletal muscle. Adherence to vascular articulations is absent [7]. Radiography depicts a discrete, soft tissue tumefaction devoid of calcification or subjacent osseous modifications [7].

Upon ultrasonography, a discrete, hypoechoic mass is denominated. Computerized tomography (CT) demonstrates a hyper-dense, poorly circumscribed tumefaction riddled with irradiating, tongue-like extensions into circumscribing soft tissue. Computerized tomography can adequately discern solitary, pulmonary parenchymal nodules or lymph node metastasis [7,8].

Primary or residual neoplasm varies from 1.3 centimetres to 3 centimetres with a mean tumour magnitude of 2.2 centimetres. The neoplasm is isointense to skeletal muscle upon T1 weighted imaging or appears hyper-intense in nearly 33% instances. Tumefaction is hyper-intense on T2 weighted and short-T1 inversion recovery (STIR) imaging [7]. MRI exhibits an infiltrative, spherical or elliptical, primary or residual neoplasm situated within subcutaneous adipose tissue. Neoplasm is hyper-intense upon fluid- sensitive MRI imaging and image enhancement following adoption of gadolinium- contrast is observed. Upon MRI, plexiform fibrohistiocytic tumour manifests as a non- nodular, plaque-like, subcutaneous tumefaction with macroscopic infiltration.

Residual neoplasm can also be exemplified following initial surgical resection [7,8].

Segregation of plexiform fibrohistocytic neoplasm upon pertinent imaging is mandated from diverse benign and malignant tumours. Benign neoplasms requiring distinction are angiolipoma, haemangioma, diffuse infiltrative or superficial plexiform neurofibroma along with phosphatase and tensin homolog (PTEN) hamartoma [3,4].

- Angiolipoma is a benign, painful, soft tissue neoplasm commonly situated within the forearm, trunk or upper extremity. Tumefaction denominates dual subcategories of common, non-infiltrating subtype with multinodular, painful nodules and the infrequent, non-encapsulated, infiltrating subtype which can invade abutting soft tissue or bone.
- Haemangioma exhibits spheroidal or tubular articulations with circumscribing septa of adipose or fibrous tissue and may be incorporated with phleboliths [3,4].
- Diffuse neurofibroma or superficial plexiform neurofibroma is an exceptional variant which delineates a reticular or plaque- like lesion confined to the subcutaneous tissue. Upon MRI, diffuse neurofibroma appears infiltrative and lacks the typical, "target- like" or "bag –of- worms" appearance exhibited by localized or plexiform neurofibroma of enlarged nerves. Around 10% diffuse neurofibromas are concurrent with neurofibromatosis type 1 [2,4].
- Phosphatase and tensin homolog (PTEN) hamartoma commonly manifest as a nodule, infrequently appears as a singular, subcutaneous lesion and delineates a predilection for soft tissue of extremities. The exceptional neoplasm may transgress fascial planes and infiltrate adjacent bone [2,3]. Malignant neoplasms with simulation of imaging characteristics mandating demarcation from plexiform fibrohistiocytic tumour are superficial, infiltrative tumefaction such as myxofibroma, undifferentiated pleomorphic sarcoma (UPS) and T cell lymphoma.
- Myxofibrosarcoma and undifferentiated pleomorphic sarcoma frequently denominate a "tail sign" comprised of peripherally dispersed, infiltrative fascicles with tumour enhancement and expansion along fascial planes. A neoplastic nodule is common [3,4].
- Peripheral T cell lymphoma is a multinodular neoplasm which can exemplify subcutaneous infiltrative manifestations.
- Haemosiderotic fibrolipomatous tumour and myxoinflammatory fibroblastic sarcoma (MIFS) enunciate a continuum of benign and malignant tumours. Haemosiderotic fibrolipomatous tumour is an infiltrative neoplasm with a predilection for subcutaneous tissue of the ankle. The tumefaction is common in middle aged adults and exhibits tumour localization and signal characteristics identical to plexiform fibrohistiocytic tumour. Regions of minimal signal intensity and "blooming artefact" at gradient-echo imaging is denominated due to hemosiderin [3,4].
- Myxoinflammatory fibroblastic sarcoma (MIFS) is a multinodular neoplasm which recapitulates tumour localization and homogenous signal enhancement of plexiform fibrohistiocytic tumour. The neoplasm demonstrates a predilection for subcutaneous tissue of distal extremities and expands along tendinous regions. High grade or dedifferentiated myxoinflammatory fibroblastic sarcoma manifests as a heterogeneous, rapidly progressive tumefaction [3,4]. MRI discernment of residual or reoccurring plexiform fibrohistiocytic tumour following resection can be challenging as tumour and postoperative alterations are identical and appear infiltrative [7].

## Therapeutic Options

Appropriate pre-operative diagnosis assists the selection of cogent surgical strategy. Comprehensive surgical resection is a primary, preferred treatment strategy. Comprehensive surgical clearance can be challenging to achieve as microscopic tumour infiltration within the subcutaneous adipose tissue and adjacent, peripheral skeletal muscle may not be discernible upon preoperative imaging. Inadequately excised, locally aggressive neoplasm is associated with localized tumour reoccurrence [7,8]. Surgical extermination of a primary or residual tumour is satisfactory. Tumour-free surgical perimeter is devoid of tumour relapse. Neoplastic remnants within a tumour perimeter can be managed with repetitive surgical resection. Absence of tumour within the periphery is defined as lack of tumour cells exceeding >0.1cm margin as discerned upon a glass slide [2,3]. Clinical and imaging (MRI) follow up from 9 months to 124 months with a mean duration of monitoring of 57months usually demonstrates an absence of tumour relapse [2,3]. Localized tumour reoccurrence is denominated in approximately 12.5% to 40% subjects. An estimated 37% of neoplasms demonstrate localized reoccurrence within 2 years of treatment. Overall percentage of tumour relapse is nearly 33% [2,3].

Around 38% tumefaction with tumour- infiltrated perimeter following initial surgery histologically confirms residual disease. Adjuvant radiotherapy can thus be gainfully employed. Adjunctive chemotherapy is usually unnecessary although is applicable in pertinent instances. Tumour metastasis is infrequent and can appear within pulmonary parenchyma or regional lymph nodes. Around 8% tumefaction metastasize to pulmonary parenchyma. Regional lymph node metastasis is discerned in an estimated 6% tumefaction [2,3].

Systemic tumour metastasis can emerge upon initial tumour discernment or appear subsequently. Pulmonary metastasis can occur at initial tumour discernment or within two years following preliminary surgery. Tumour mortality is absent [7,8].

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9. Image 1 and 2 Courtesy: Basic medical key

10. Image 3 Courtesy: Pathology outlines

11. Image 4 Courtesy: JAMA network

12. Image 5 Courtesy: Humpath.com

13. Image 6 Courtesy: Twitter.com

14. Image 7 Courtesy: Core.com

15. Image 8 Courtesy: Webpathology.com