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Editorial

The Acral Alternative-Myxoinflammatory Fibroblastic Sarcoma

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Preface

Myxoinflammatory fibroblastic sarcoma is an exceptional, low grade, fibroblastic sarcoma with a typical acral representation and an inflammatory cellular infiltrate with innumerable eosinophils. Initially scripted by Montgomery., *et al*. in 1998, myxoinflammatory fibroblastic sarcoma is additionally designated as acral myxoinflammatory fibroblastic sarcoma or inflammatory myxohyaline tumour of distal extremities with virocyte or Reed-Sternberg-like cells [1].

Tumefaction predominantly arises within hands and feet and is composed of a myxoid stroma enveloping diverse inflammatory and virocyte-like cells. The neoplasm can be misinterpreted as an infectious or non-neoplastic inflammatory process or pigmented villonodular tenosynovitis.

Disease pathogenesis

Viruses such as Epstein Barr virus, cytomegalovirus (CMV) and herpes simplex virus (HSV) are usually not implicated in engenderment of the neoplasm [2,3].

Genomic rearrangement of TGFBR3 and MGEA5 genes are documented in myxoinflammatory fibroblastic tumour, haemosiderotic fibrolipomatous tumour, pleomorphic hyalinising angiectatic tumour and hybrid neoplasms [3,4].

Myxoinflammatory fibroblastic sarcoma is contemplated to be associated with chromosomal translocation t(1;10). Repetitive genomic translocation t(1;10)(p22;q24) incriminating TGFBR3 and MGEA5 genes is documented along with upregulation of adjacent genes FGF8 and NPM3. A subset of neoplasms harbour recurrent genomic amplification of 3p11.1-12.1 region appearing as marker or ring chromosomes. Additionally, enhanced expression of VGLL3 (3p12.1) and CHMP2B (3p11.2) is commonly associated with aforesaid genomic amplification [3,4].

An estimated 22% of neoplasms depict BRAF chromosomal mutation. Neoplasms with BRAF genetic rearrangement or amplification are commonly delineated in adults between36 years to 74 years with a mean age at 53 years [3,4].

A mild male predominance is exemplified with a male to female proportion of 4:3. A predilection for acral region is enunciated such as finger or foot although non-acral sites such as the wrist, forearm and knee can be implicated. Besides, subcutaneous tissue, tendon sheaths and intra-articular zones can depict the neoplasm [3,4].

Neoplasms with BRAF genomic alterations depict tumour cells with vesicular nuclear chromatin and prominent nucleoli along with variable quantities of Reed-Sternberg-like cells [3,4].

Neoplasms with TGFBR3 or MGEA5 chromosomal rearrangements display diverse patterns of nuclear chromatin such as vesicular, fine or hyperchromatic. Also, Reed-Sternberg-like cells may be minimal. Tumefaction may exhibit fascicles of elongated, spindle-shaped cells admixed with the typical tumour pattern [3,4].

Tumours with BRAF alterations are common within upper extremities whereas neoplasms with TGFBR3 and MGEA5 genetic rearrangements are frequent within lower extremities [3,4].

Disease characteristics

Majority of neoplasms are situated within the subcutaneous tissue and tumefaction may extensively infiltrate superficial and deep-seated soft tissue. Typically, the neoplasm appears as a singular, lobulated nodule or multiple, poorly demarcated tumour nodules admixed with fibro-connective tissue septa. Tumefaction is enmeshed within subcutaneous adipose tissue, fascial planes or tendon sheaths. Neoplasm may incriminate the dermis or infiltrate skeletal muscle [5,6].

Acral sites as the distal extremities, hands or feet are incriminated in a majority (77%) of instances. A subset of lesions may arise within axial sites. The neoplasm is observed in adults with a mean age of disease emergence at 48 years [5,6].

Tumour cells depict complex and heterogeneous karyotypes along with foci of cellular aneuploidy, ring chromosomes, genetic translocation t(2;6) and t(1;10)(p22;q24) with consequent genomic rearrangements of TGFBR3 and MGEA5 genes [5,6].

Clinical elucidation

The neoplasm manifests as a gradually progressive, solitary nodule situated at acral sites such as base of finger or wrist with minimal infiltration into abutting soft tissue or emerges as a multinodular mass [5,6].

The neoplasm is associated with an indolent clinical course, a significant delay in tumour discernment prior to excision, enhanced possibility of localized tumour reoccurrence and absent distant metastases [5,6].

Histological elucidation

Fragments of the tumefaction are firm, rubbery, nodular or lobulated and appear grey, light tan or yellow pink. Tumour magnitude varies from 0.5 centimetre to 15 centimetres with mean diameter of 3.2 centimetres and median diameter of 2.4 centimetres. Focal necrosis and cyst formation may be discerned.

Grossly, multiple nodules of a poorly demarcated, miniature neoplasm is observed which frequently incriminates joints and tendons. Cut surface is gelatinous, mucoid, whitish or grey/white with myxoid areas and foci of fibrosis [5,6].

On cytological examination, spindle-shaped, epithelioid, lipoblast-like and ganglion-like cells are observed entangled within a myxoid stroma and a prominent infiltrate of inflammatory cells such as neutrophils, lymphocytes, histiocytes and eosinophils [5,6].

On microscopy, majority (75%) of instances display a stromal matrix composed of fibro-sclerotic stroma intermingled with miniature, mucin-rich pools. Myxoid zone is enlarged and segregated by bands of fibro-sclerotic tissue or traversed by bulbous, hyalinised, fibro-connective tissue septa. Foci of abundant vascular articulations, akin to granulation tissue are observed [6,7].

Tumour cellularity and composition is variable and neoplasms may be minimally, moderately or extensively cellular. Alternating solid and myxoid tumour foci with a prominent inflammatory infiltrate and Reed-Sternberg-like cells with macro-nucleoli are admixed with plump, spindle shaped or epithelioid tumour cells [6,7].

Tumour is composed of plump, spindle-shaped cells with fibrillary cytoplasm or epithelioid, histiocyte-like cells with enlarged, vesicular nuclei, peripheral nuclear chromatin and distinct, eosinophilic nucleoli. Intra-nuclear cytoplasmic inclusions are significant. Histiocytoid or epithelioid tumour cells demonstrate plump vesicular nuclei, distinct nucleoli and variable eosinophilic cytoplasm [6,7].

The nodular tumefaction depicts a mildly infiltrative tumour perimeter invading into adjacent subcutaneous adipose tissue and dermis although abutting skeletal muscle is infrequently involved. Tumour is predominantly constituted of acute and chronic inflammatory cells comprised by solid sheets of histiocytoid or epithelioid cells with vesicular chromatin and prominent nucleoli [6,7].

Inflammatory cells such as lymphocytes and plasma cells with occasional lymphoid aggregates are evenly disseminated within the tumour cells. A focal, extra-cellular myxoid matrix is admixed with solid areas. Characteristic Reed-Sternberg-like tumour cells with macronucleoli are commingled with sheets of histiocytoid cells, an intense infiltrate of inflammatory cells and myxoid areas. Enlarged tumour cells with smudgy chromatin and foci of emperipolesis are observed [7].

The neoplasm is multinodular, inadequately circumscribed and is composed of a polymorphous inflammatory component intermingled with varying proportions of fibrosis, stromal hyalinization and myxoid stroma. Inflammatory infiltrate is variable and is constituted by lymphocytes, plasma cells, eosinophils, neutrophils and histiocytes. Tumour foci may recapitulate malignant fibrous histiocytoma [6,7].

Prominent foci of myxoid alteration are observed. Proportion of myxoid zone is variable and may arise as focal myxoid area within a predominantly solid tumefaction, multiple myxoid nodules or diffuse myxoid stroma in combination with or absence of intense vascularity. Preponderantly, the myxoid component is incorporated with singular and disseminated tumour cells. However, a cord-like or reticular tumour pattern may also be discerned. Collagenous stroma may be prominent and appears intermixed with the myxoid areas [6,7].

Significant nuclear pleomorphism or absence of myxoid areas can be observed.

Tumour cells are denominated by enlarged, atypical fibroblastic cells. Few tumour cells display macro-nucleoli and simulate Reed-Sternberg-like cells. Epithelioid tumour cells are imbued with abundant, eosinophilic cytoplasm and an enlarged nucleus. The nucleus may be incorporated with a viral inclusion body-like nucleolus or smudged heterochromatin. Multi-vacuolated fibroblasts are imbued with mucoid or myxoid substance and are designated as pseudo-lipoblasts, a few of which display enlarged nuclei and nucleoli. Characteristic, atypical ganglion-like cells can be absent or obscured by an intense inflammatory infiltrate. Foci of coagulative necrosis are discerned [6,7].

Lympho-plasmacytic inflammatory infiltrate may be intense, organized into discrete follicles, circumscribe vascular articulations, accumulate at tumour periphery or infiltrate cellular aggregates [6,7].

Neutrophils may configure a micro-abscess, eosinophils can be preponderant, histiocytes may articulate multinucleated cells simulating osteoclasts, clusters or sheets of xanthomatous histiocytes and Touton-like giant cells may be discerned. Emperipolesis of neutrophilic inflammatory cells is occasionally observed. Hemosiderin deposition can be considerable and fibrin deposits are documented. Hemosiderin-laden macrophages are scattered in a perivascular distribution [6,7].

Mitotic activity can be absent or vary from one to five mitosis per 10 high power fields. Atypical mitosis may be encountered [7].

On ultrastructural examination, tumour cells are represented by fibroblastic cells with abundant rough endoplasmic reticulum, mitochondria and intermediate filaments [6,7].

Lipoblast- like cells delineate cytoplasmic pseudo-inclusions with extra-cellular mucin [6,7].

Immune histochemical elucidation

Tumour cells are variably immune reactive to CD34, CD68, CD163, CD117, vimentin, epithelial membrane antigen (EMA) and epidermal growth factor receptor (EGFR). Proliferative index Ki-67 is minimal [3,4].

Tumour cells with macro-nucleoli are immune non reactive to CD15, CD30 and CD45. Genetic rearrangements of TGFBR3 or MGEA5 can be observed [3,4].

Differential diagnosis

Myxoinflammatory fibroblastic sarcoma requires a segregation from diverse conditions such as:

- Extranodal Hodgkin lymphoma is a condition which is accompanied by generalized lymph node enlargement. Reed- Sternberg cells are engendered from and admixed with lymphoid cells. Reed- Sternberg cells are immune reactive to CD15 and CD30. Neutrophils are uncommon. An absence of giant cells, lipoblast-like cells and myxoid areas is discerned [8,9].

- Pigmented villonodular tenosynovitis is additionally denominated as tenosynovial giant cell tumour. Tumefaction is frequently discerned within the knee joint of young females. Subsynovial nodules are composed of cells incorporated with abundant cytoplasm and pale-staining nuclei. Tumour cells are admixed with multinucleated giant cells, foamy macrophages and haemosiderin-laden macrophages [8,9].

- Haemosiderotic fibrohistiocytic lipomatous tumour is a neoplasm composed of bland, spindle-shaped cells subdivided by fibrous tissue septa with infiltration of abutting adipose tissue along with the articulation of a distinct “honeycomb” pattern. Abundant haemosiderin pigment deposition is observed within the histiocytic cells. Cellular and nuclear atypia is absent and mitotic figures are below < 1 mitosis per ten high power fields. Stroma is focally myxoid with scattered osteoclast-like multinucleated giant cells and thrombosed vascular configurations. The neoplasm is variably circumscribed by a component of mature adipose tissue. Tumefaction is generally observed within distal extremities [8,9].

- Viral infection is demonstrated by multinucleated, acantholytic keratinocytes with distinct nuclear inclusions initially confined to the follicular epithelium. Epidermal necrosis and extensive acantholysis is delayed. Perineural infiltrate of lymphocytes and neutrophils is enunciated within the dermal nerves. Schwann cell hypertrophy and neural necrosis is occasional [8,9].

- Myxofibrosarcoma is exceptionally discerned within soft tissues of hands and feet. The multinodular neoplasm is composed of pleomorphic spindle-shaped cells entangled within a myxoid background. Curvilinear vascular articulations with circumscribing condensed tumour cells are characteristic. Intervening fibrous tissue septa are incomplete and myxoid stroma is infiltrated with immature dendritic reticulum cells. Solid tumour foci are observed. Mitotic figures are frequent with exemplification of atypical mitosis. An absence of inflammatory infiltrate is observed. High grade tumours are cellular with focal haemorrhage, necrosis and bizarre, multinucleated giant cells [8,9].

- Epithelioid sarcoma is a neoplasm presenting as a dermal or subcutaneous nodule and simulates a granulomatous process. Tumefaction is composed of uniform, plump, miniature to medium sized cells with eosinophilic cytoplasm. Tumour nodule depicts peripheral aggregates of spindle-shaped cells. Mitotic activity is variable. Tumour cells are admixed with a chronic inflammatory infiltrate. Foci of dystrophic calcification and metaplastic bone may be enunciated. The neoplasm is intensely immune reactive to cytokeratin and depicts loss of INI1/ SMARCB expression [8,9].

- Rosai Dorfman disease is a condition where emperipolesis is commonly discerned although myxoid areas and intra-nuclear viral-like inclusions are absent. Plasma cells are abundant and numerous Russell bodies are discerned along with distended nodal sinuses, capsular and peri-capsular inflammation and fibrosis. Plasma cells circumscribe venules with prominent endothelium. Tumour cells are immune reactive to CD30, CD14, CD68 and S100 protein [8,9].

- Pleomorphic liposarcoma is a well circumscribed, non encapsulated, infiltrative neoplasm composed of true pleomorphic lipoblasts. Enhanced mitotic activity of around 25 mitosis per 10 high power fields along with atypical mitotic figures and an absence of accompanying inflammatory infiltrate is discerned. The high grade neoplasm depicts tumour cells imbued with enlarged, spherical or bizarre nuclei [8,9]. Haemangiopericytoma-like foci and extracellular and intracellular hyaline droplets are observed. The neoplasm is exceptionally exemplified within soft tissues of hands and feet [8,9].

- Tenosynovitis is an inflammatory condition where constituent enlarged, atypical cells are absent [9].

Therapeutic options

Myxoinflammatory fibroblastic sarcoma can be adequately treated by localized surgical excision with a wide periphery of normal, uninvolved tissue. Radiation therapy may or may not be necessitated [8,9].

Localized tumour reoccurrence is common, especially in neoplasms composed of tumour cells with prominent atypical nuclei. Distant tumour metastasis are exceptional and are observed in around 1% instances. Tumours depicting localized reoccurrence can be subjected to comprehensive surgical extermination with a broad perimeter of uninvolved soft tissue and adjuvant radiation therapy [8,9].

Neoplasms with BRAF genetic mutation depict a propensity for localized tumour reoccurrence in the absence of distinct distant metastasis and may be treated by comprehensive surgical eradication with a broad perimeter of normal tissue and neoadjuvant chemotherapy. Repetitive surgical excision may be employed, if required [8,9].

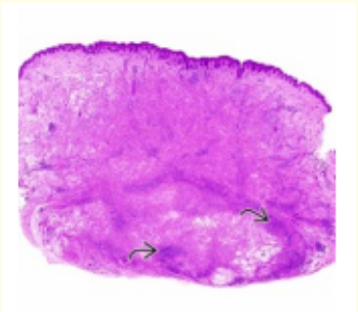

Figure 1: *Myxoinflammatory fibroblastic sarcoma depicting a multinodular appearance with foci of fibrosis and a superimposed atrophic epidermal layer [10].*

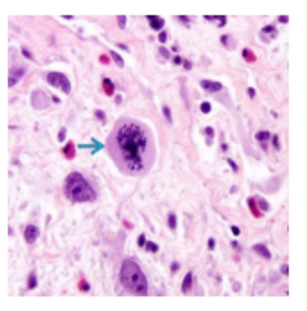

Figure 2: *Myxoinflammatory fibroblastic sarcoma delineating plump, spindle-shaped cells admixed with inflammatory cells as the neutrophils, lymphocytes eosinophils and mitotic figures [10].*

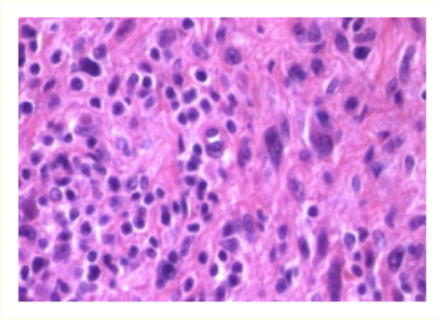

Figure 3: *Myxoinflammatory fibroblastic sarcoma demonstrating plump spindle-shaped cells admixed with variable inflammatory cells as mature lymphocytes, neutrophils, eosinophils and virocyte-like cells scattered in a dense, fibrotic stroma [11].*

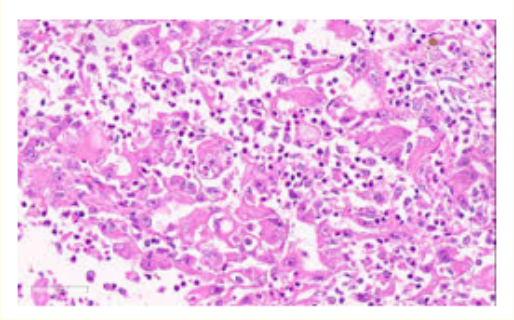

Figure 4: *Myxoinflammatory fibroblastic sarcoma depicting an intense inflammatory exudate of neutrophils, lymphocytes, eosinophils and giant cells intermingled with spindle-shaped cells and focal fibrosis [12].*

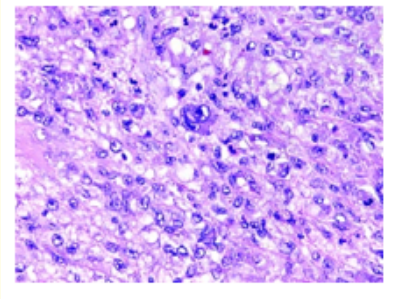

Figure 5: *Myxoinflammatory fibroblastic sarcoma exemplifying spindle-shaped intermingled with inflammatory cells as mature lymphocytes, histiocytes, neutrophils and few giant cells scattered in a fibrotic stroma [13].*

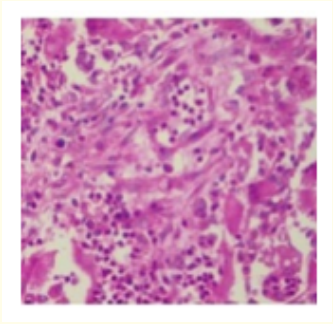

Figure 6: *Myxoinflammatory fibroblastic sarcoma exhibiting fascicles of spindle-shaped enmeshed within a fibrous tissue stroma with numerous lymphocytes, eosinophils, neutrophils and histiocytes [14].*

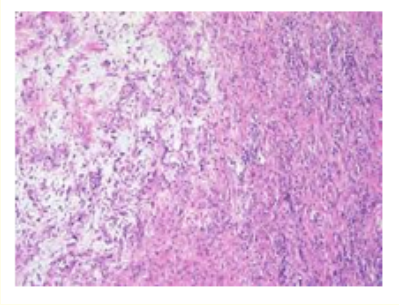

Figure 7: *Myxoinflammatory fibroblastic sarcoma enunciating bands of spindles-shaped cells intermixed with inflammatory cells such as lymphocytes, histiocytes and neutrophils enmeshed within a fibrotic stroma [15].*

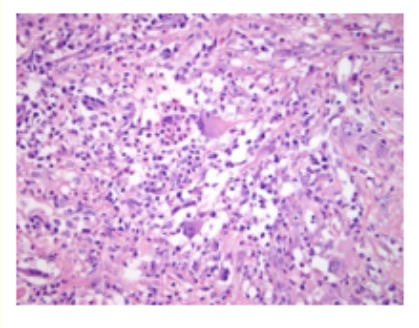

Figure 8: *Myxoinflammatory fibroblastic sarcoma delineating spindle-shaped cells commingles with Reed-Sternberg-like giant cells, lymphocytes, neutrophils and eosinophils [16].*

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