The Protracted Whorls-Epithelioid Fibrous Histiocytoma

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ABSTRACT
Epithelioid fibrous histiocytoma is an exceptional, enigmatic variant of cutaneous benign fibrous histiocytoma delineating a characteristic morphology and immune-phenotype. Epithelioid fibrous histiocytoma was initially scripted as an unknown variant of fibrous histiocytoma and designated as “Epithelioid Cell Histiocytoma”[1]. Currently, Epithelioid fibrous histiocytoma is contemplated to be an established variant of benign fibrous histiocytoma, especially a dermatofibroma. Besides, the distinctive, non-destructive neoplasm manifests as an unrelated category of mesenchymal tumefaction. The neoplasm is additionally denominated as epithelioid dermatofibroma and mandates a distinction from diverse benign and malignant mesenchymal lesions. Genomic rearrangement of Anaplastic Lymphoma Kinase (ALK) with concomitant enunciation of ALK protein designates the neoplasm to be biologically distinct from conventional benign fibrous histiocytoma and variants.

Keywords: Epithelioid fibrous histiocytoma; Anaplastic Lymphoma Kinase (ALK)

INTRODUCTION
Disease characteristics
Tumefaction is frequently situated within the extremities and trunk wherein lesions within head and neck are infrequent. The neoplasm is commonly denominated within the lower extremities (78%), thigh (30%), upper extremities (20%), trunk (10%) and head and neck (<10%) [2-3]. Adult population is usually implicated. The neoplasm is frequently delineated within the fifth decade and can appear within third to seventh decades. Incriminated subjects demonstrate a mean age of disease occurrence at 39 years and disease appearance between 8 years to 74 years [2-3]. An equivalent gender predisposition or a slight male predominance is observed with a male to female proportion of 1.4:1 [2-3]. Typically, the neoplasm depicts cytoplasmic immune reactivity to Anaplastic Lymphoma Kinase (ALK). Additionally, majority (88%) of neoplasms depict chromosomal translocation of ALK gene discernible with Fluorescence In Situ Hybridization (FISH). A subset of tumours depict clone-specific genetic rearrangements [2-3].

Genetic elucidation
Anaplastic Lymphoma Kinase (ALK) or CD246 encodes a transmembrane receptor tyrosine kinase within the insulin receptor superfamily. Genetic alterations constituted by chromosomal translocation, mutation, copy number modification and dysregulated expression are observed in several categories and diverse neoplasms. Next-generation sequencing demonstrates VCL and SQSTM1 as distinctive fusion partners of ALK gene [2-3]. ALK gene may exemplify fusion with several partner genes which results in divergent clinical behavior. Disparate neoplasms may incorporate identical fusion partners. Frequently delineated genomic fusion partners of ALK gene are SQSTM1 (52%) and VCL (30%) with concurrent fusion products. Additionally, novel fusion partners such as DCTN1, ETV6, PPFIBP1, and SPECC1L are observed. Fusion breakpoint generally incriminates exon 20 of ALK gene. Occurrence of cogent genetic fusion products can be confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) [2-3]. As SQSTM1 and VCL are prevalent fusion partners of ALK gene, SQSTM1-ALK is a common fusion product delineated in an estimated >50% of epithelioid fibrous histiocytomas. Greater than one-third (<33%) of tumours manifest VCL-ALK fusion product. VCL encodes vinculin which is an adhesion protein combining extracellular matrix to actomyosin cytoskeleton. Vinculin is implicated in cellular migration, cell-matrix adhesion and cell-cell junctions [3-4]. In addition, novel fusion partners to ALK gene are DCTN1, ETV6, PPFIBP1 and SPECC1L. ETV6-ALK and SPECC1L-ALK fusion genetic products are also observed [3-4]. DCTN1-ALK genomic fusion occurs in epithelioid fibrous histiocytoma. DCTN1 encodes the dynactin subunit 1 which is a mammoth subunit of dynactin complex and binds microtubules with cytoplasmic dynein. Dynactin is a microtubule-based biological interactor with diverse cellular functions such as cell division and
mobility of intracytoplasmic vesicular and organelles [34]. ETV6-ALK fusion product in epithelioid fibrous histiocytoma is associated with nuclear pattern of ALK immunoreactivity. ETV6 (TEL) or ETS Variant 6 encodes an E-Twenty-Six (ETS) family transcription factor implicated in DNA configuration and protein binding. The gene contributes to critical functions in cellular development, differentiation and cellular proliferation [34]. Genetic translocation of PPFIBP1-ALK is reported in epithelioid fibrous histiocytoma. PPFIBP1 encodes PPFIA Binding Protein1 (liprin-β1) which is a Leukocyte Common Antigen-Related (LAR) protein-tyrosine phosphatase-interacting protein. The protein is implicated in cell adhesion, migration and cellular development [34]. SPECC1L (Sperm Antigen with Calponin Homology and Coiled-Coil Domains1) encodes a cytoskeletal cross-linking protein and is implicated in cellular adhesion, mobility and cell division [34]. An association between tumour morphology and concordant ALK fusion partner genes is absent. Neoplasms with SQSTM1-ALK fusion and VCL-ALK fusions can be morphologically and immunohistochemically identical. ALK genetic fusion with novel fusion partners may demonstrate polypoid lesions. Tumours can be ulcerated and delineate a mixed epithelioid cell and spindle-shaped cell morphology. Immunohistochemistry for ALK may display diffuse, granular, cytoplasmic staining or singularly nuclear staining [34]. Morphologically, neoplasms with SPECC1L-ALK genetic fusion occurs in epithelioid fibrous histiocytoma. SPECC1L (Sperm Antigen with Calponin Homology and Coiled-Coil Domains1) encodes a cytoskeletal cross-linking protein and is implicated in cellular adhesion, mobility and cell division [34]. An association between tumour morphology and concordant ALK fusion partner genes is absent. Neoplasms with SQSTM1-ALK fusion and VCL-ALK fusions can be morphologically and immunohistochemically identical. ALK genetic fusion with novel fusion partners may demonstrate polypoid lesions. Tumours can be ulcerated and delineate a mixed epithelioid cell and spindle-shaped cell morphology. Immunohistochemistry for ALK may display diffuse, granular, cytoplasmic staining or singularly nuclear staining [34]. Morphologically, neoplasms with SPECC1L-ALK genetic fusion occurs in epithelioid fibrous histiocytoma. SPECC1L (Sperm Antigen with Calponin Homology and Coiled-Coil Domains1) encodes a cytoskeletal cross-linking protein and is implicated in cellular adhesion, mobility and cell division [34]. An association between tumour morphology and concordant ALK fusion partner genes is absent. Neoplasms with SQSTM1-ALK fusion and VCL-ALK fusions can be morphologically and immunohistochemically identical. ALK genetic fusion with novel fusion partners may demonstrate polypoid lesions. Tumours can be ulcerated and delineate a mixed epithelioid cell and spindle-shaped cell morphology. Immunohistochemistry for ALK may display diffuse, granular, cytoplasmic staining or singularly nuclear staining [34].

Clinical elucidation

The neoplasm is contemplated to arise from the dermal microvascular unit. Clinically, lesions simulate pyogenic granuloma and appear as miniature and solitary. The uncommon neoplasm is composed of flesh coloured, elevated nodules varying from 0.5 cm to 2.0 cm magnitude. Epithelioid fibrous histiocytoma represents as an exophytic nodule or a dermal neoplasm. Tumefaction can simulate a melanocytic, vascular, epithelial or associated histiocytic neoplasm [4-5]. The neoplasm commonly manifests as a solitary, polypoid, minimally elevated, symmetrical, reddish papule or nodule. Exceptionally, multi-centric lesions are denominated [4-5].

Histological elucidation

Epithelioid fibrous histiocytoma demonstrates a well circumscribed, exophytic tumefaction centred upon the dermis with a superimposed collarette of stratified squamous epithelium [5-6]. Typically, tumefaction is composed of an estimated 50% of epithelioid or spherical cells which constitute the proliferating cellular component. Upon low-power magnification, the neoplasm depicts distinctive tumour configuration as denominated by well defined, exophytic cellular proliferation confined to the papillary and superficial reticular dermis and by minimally circumscribed cellular proliferation with extension into the deep-seated dermis and superficial subcutaneous adipose tissue [5]. On microscopy, the neoplasm appears as a polypoid lesion which is superimposed with a collarette of epidermal tissue. Clusters or expanse of angulated, epithelioid cells imbued with abundant, eosinophilic cytoplasm are enunciated. The tumour is devoid of junctional activity or cellular theques. Multinucleated giant cells and foamy macrophages or xanthoma cells are admixed with vascular channels [5-6]. Tumefaction is comprised of plump, epithelioid cells occasionally admixed with a spindle cell component. Tumour cell nuclei are spherical to ovoid, with vesicular chromatin and minimal atypia. Disseminated bi-nucleated and tri-nucleated cells are observed. Mitotic activity is minimal [5-6]. Tumefaction is composed of sheets of epithelioid cells configuring a focal storiform pattern. Individual tumour cells are incorporated with abundant eosinophilic cytoplasm, spherical vesicular nuclei and prominent nucleoli. Tumour cells may be significantly enlarged and demonstrate nuclear atypia. An accompanying inflammatory cell infiltrate is frequently observed along with few mitotic figures. Multinucleated giant cells are exceptional and hemosiderin pigment deposits can be discerned [5-6]. Tumour cell aggregates may be segregated from the epidermis by a Grenz zone and exhibit an irregular peripheral tumour margin. Generally, the neoplasm lacks a tumour-free zone between epidermis and dermis and is composed of an estimated 50% tumour cell population of spherical or polygonal epithelioid cells imbued with abundant, eosinophilic cytoplasm, spheroidal to elliptical, vesicular nuclei with miniature eosinophilic nucleoli. Mild nuclear pleomorphism is observed. Varying percentage of bi-nucleate or tri-nucleate cells are disseminated amidst the epithelioid cells. Multinucleated giant cells are exceptional. Mitotic figures appear at an average of one mitosis per 10 high-power fields [5-6]. The frequently exophytic neoplasm is well circumscribed and demonstrates an epidermal collarette. As the tumefaction is composed of uniform, medium to enlarged, angulated epithelioid cells which comprise of an excess of 50% of neoplastic cells, distribution of tumour cells is frequently perivascular. Several bi-nucleated cells are exemplified. Tumour periphery may depict typical features of dermatofibroma. Accompanying inflammation is minimal [5-6]. Frequently, epidermal collarette encompasses the lesion and can extend to the base of the lesion. Superimposed stratified squamous epithelium can be hyperplastic, atrophic or delineate an admixture of aforesaid morphologies [5-6]. Numerous miniature vascular articulations are dispersed amongst epithelioid cell clusters wherein a predominance of vascular component can recapitulate a vascular lesion. Antecedent lesions are enmeshed within a delicate collagenous stroma whereas ancient neoplasms appear hyalinised. Myxoid alterations can be prominent and predominant [5-6]. The neoplasm is devoid of admixed cutaneous adnexal structures. Focal areas of typical benign fibrous histiocytoma are discerned [6, 10-15] (Figures 1-6).
Figure 2: Epithelioid fibrous histiocytoa depicting fascicles of epithelioid cells with eosinophilic cytoplasm divided by fibro-connective tissue septa.

Figure 3: Epithelioid fibrous histiocytoa delineating whorls of plump epithelioid cells with eosiinophilic cytoplasm and vesicular nuclei subdivided by fibrous tissue septa.

Figure 4: Epithelioid fibrous histiocytoa depicting whorls of epithelioid cells with abundant cytoplasm and encompassing fibrous tissue septa.

Figure 5: Epithelioid fibrous histiocytoa exhibiting plump, epithelioid cells with abundant, eosinophilic cytoplasm, vesicular nuclei and enveloping delicate stroma.

Figure 6: Epithelioid fibrous histiocytoa delineating eddies of epithelioid cells clusters encompassed by fibrous tissue septa and a superimposed layer of stratified squamous epithelium.

Figure 7: Epithelioid fibrous histiocytoa demonstrating whorls of plump, epithelioid cells with abundant, eosinophilic cytoplasm and vesicular nuclei with traversing fibrous tissue septa.

Figure 8: Epithelioid fibrous histiocytoa immune reactive to ALK.

Immune histochemical elucidation

Tumour cells are immune reactive to Factor XIIIa, vimentin, CD163 and variably immune reactive to CD68. Vascular articulations are immune reactive to CD31 and CD34. An admixture of dendritic histiocytes immune reactive to Factor XIIIa and dermal fibroblasts immune reactive to CD34 is exemplified. An estimated two thirds (66%) of neoplasms are immune reactive to Epithelial Membrane Antigen (EMA) and around 50% tumours are immune reactive to D2-40 [2-3]. Tumour cells are immune non reactive to S100 protein, high and low molecular weight cytokeratin, CD31, CD68, Smooth Muscle Actin (SMA), Desmin, Myogenin or Associated myogenic immune markers and Human Melanoma Black 45 (HMB-45) Antigen [2-3]. Majority of neoplasms depict a cytoplasmic immune reactivity to Anaplastic Lymphoma Kinase (ALK). The neoplasm demonstrates genome translocation of Anaplastic Lymphoma Kinase1 (ALK-1) which can be discerned with Fluorescent In Situ Hybridization (FISH) [2-3]. On immunohistochemistry, ALK immune reactivity appears as granular cytoplasmic staining (52%), granular cytoplasmic staining in combination with nuclear staining (43%) and singular nuclear staining (4%). SQSTM1-ALK genetic fusion is concordant with granular cytoplasmic and nuclear ALK staining (75%) whereas VCL-ALK genetic fusion is generally associated with granular cytoplasmic immunoreactivity in the absence of nuclear staining (86%). ETV6-ALK fusion is accompanied by singular nuclear staining whereas adjacent novel fusion partners depict granular cytoplasmic staining [2-3].

Differential diagnosis

Epithelioid fibrous histiocytoa requires a segregation from Malignant Melanoma wherein the variant of amelanotic malignant melanoma is composed of enlarged, pleomorphic epithelioid cells appearing in association with incriminated superimposed stratified squamous epithelium. Malignant melanoma is comprised of dense clusters of atypical cells. The neoplasm is immune reactive to S100 protein and Human Melanoma Black 45 (HMB-45) antigen [7-8].

Epithelioid Sarcoma is a deep-seated neoplasm and constituted of aggregates of epithelioid cells configuring a granuloma. Foci of tumour cell necrosis along with cellular and nuclear atypia are observed. The neoplasm is immune reactive to keratin and immune non reactive to CD163 [7-8].

Epithelioid Cell Granuloma is composed of epithelioid histiocytes accumulated in well configured cellular clusters with a circumscripture of mature lymphocytes [7,8].

Histiocytic Sarcoma is an exceptional neoplasm composed of epithelioid histiocytic cells demonstrating significant cellular and nuclear atypia and prominent mitotic activity. No site of disease emergence is exempt and virtually the body viscera and organs may be afflicted in entirety [7-8].

Rosai-Dorfman’s disease is comprised of multiple cutaneous lesions appearing in combination of generalized lymphadenopathy. Engendering histiocytic cells are immune reactive to S100 protein,
are pleomorphic and display foci of emperipolesis. Additionally, admixed B lymphocytes and plasma cell infiltrate is prominent [7-8]. Solitary Epithelioid Histiocytoma is constituted by cells imbued with dense, cosinophilic and glassy cytoplasm, frequent spiked cytoplasmic projections, variable nuclear grooves and an admixture of multinucleated giant cells. Infiltration of lymphocytes and neutrophils is frequently observed. Tumour cells are immune reactive to CD68 and CD163 [7-8].

Dermal Neoplasms with a constituent of epithelioid cells such as vascular, smooth muscle or histiocytic tumours with epithelioid cell component can be adequately segregated with cogent immunohistochemistry [8-9].

Spitz nevus is composed of nevroid subtype of cellular clusters accumulated at the tumour periphery. A spindle-shaped and epithelioid cellular component is commingled within the nevroid cell clusters. Tumour cells depict significant atypia, variable mitotic activity and scanty pigmentation. Deep-seated tumour cells demonstrate cellular maturation. Enlarged, distinctive Kamino bodies or eosinophilic, hyaline bodies are dispersed along the dermo-epidermal junction. Tumour cells are immune reactive to S100 protein [7-8].

Reticulohistiocytoma depicts a diffuse infiltration of numerous enlarged, mononuclear or multinucleated histiocytes confined to the dermis. A lymphocytic infiltrate is observed along with foci of dermal fibrosis. Tumour cells depict a dense, “ground glass” or oncocytic cytoplasm. Tumour cells are immune reactive to CD68 and Factor XIIIa and immune non reactive to S100 protein and CD1a [7-8].

Juvenile Xanthogranuloma exemplifies a dense proliferation of lympho-histiocytic inflammatory cells confined to the dermis. Foamy macrophages and Touton giant cells are intermingled within the dermal lympho-histiocytic inflammatory infiltrate. Miniature fascicles of spindle-shaped cells are delineated along with fibro-histiocytic cells and foci of fibrosis. Mitotic figures are absent. The neoplasm is immune reactive to CD68, lysozyme, vimentin, Factor XIIIa and immune non reactive to S100 protein and CD1a [7-8].

Epithelioid Perineurioma is composed of an admixture of bland, elongated and epithelioid cells configuring parallel bundles. Tumefaction simulates a neurofibroma or may depict a storiform or a fascicular pattern of tumour evolution. Collagenous stroma encompasses tumour cell aggregates and demonstrates peri-cellular clefts. Cellular or nuclear atypia and mitotic activity is exceptional [7-8].

Therapeutic options

Tumefaction can be adequately alleviated with a simple surgical extermination. Localised tumour recurrence following inadequate surgical eradication is exceptional [8-9].

REFERENCES

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