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Guest Editorial

The Neoplastic Infectivity-Inflammatory Myofibroblastic Tumour

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Preface

Inflammatory myofibroblastic tumour is a neoplasm of myofibroblastic origin demonstrating an inflammatory infiltration composed of plasma cells, lymphocytes and eosinophils. An exceptional, heterogeneous group of lesions comprised predominantly of myofibroblastic and fibroblastic, spindle-shaped cells interspersed with chronic inflammatory cells denominate the neoplasm. Inflammatory myofibroblastic tumour is a tumour of intermediate biological potential, thus designated due to potential for localized tumour reoccurrence and minimal proportion of distant metastasis.

The neoplasm is additionally designated as inflammatory fibrosarcoma, inflammatory pseudo-tumour or plasma cell granuloma. Inflammatory myofibroblastic tumour was initially scripted by Brunn., *et al*. in 1939 as a pulmonary lesion [1]. The neoplasm appears in younger individuals and is associated with deregulation of anaplastic lymphoma kinase (ALK) gene. Tumefaction can be multifocal and is commonly discerned within retroperitoneum, omentum, mesentery, pulmonary parenchyma, gastrointestinal tract, genitourinary tract or associated sites.

Disease pathogenesis

Of uncertain pathogenesis, inflammatory myofibroblastic tumour demonstrates repetitive, clone-specific, genetic rearrangements of chromosome 2p. Also, chromosomal rearrangements of ALK gene are discerned in excess of > 50% instances.

Immunoglobulin G4 (IgG4)- related disease is commonly associated with neoplasms arising within head and neck [2,3].

Concurrence of trauma, chronic inflammation or autoimmune disease is observed, features which are indicative of a reactive process.

Production of interleukin 6 messenger ribonucleic acid (IL-6 mRNA) and protein by tumour cells is posited to engender systemic symptoms in inflammatory myofibroblastic sarcoma [2,3].

Occurrence of prominent inflammatory infiltrate and associated systemic symptoms may suggest a viral aetiology of inflammatory myofibroblastic tumour. Viral infection with Epstein Barr virus (EBV), human immune deficiency virus (HIV) and human herpes virus 8 (HHV8) is delineated, although is infrequent within lesions of head and neck. However, classic sites of the neoplasm exceptionally exemplify presence of Epstein-Barr virus (EBV). Discernment of deoxyribonucleic acid of human herpes virus 8 (HHV8- DNA) within pulmonary and extra-pulmonary lesions is controversial [2,3].

Disease characteristics

The neoplasm delineates a predilection for children, adolescents or young adults and demonstrates a mean age of disease emergence at 10 years, although tumefaction can occur up to eighth decade. Primary tumours can arise within 17 months to 79 years although middle aged or elderly subjects are infrequently incriminated.

Frequently, tumefaction is anatomically distributed within abdominopelvic region, retroperitoneum or pulmonary parenchyma although somatic soft tissue, bone, larynx, uterus and central nervous system are also implicated [2,3].

The neoplasm depicts a strong predilection for emerging within viscera and deep-seated soft tissues of abdomen, pelvis, mesentery, retroperitoneum, mediastinum, iliac bone, neck, forearm, pulmonary or hepatic parenchyma. Maxillofacial region is rarely incriminated although epiglottis, endolarynx, parapharyngeal space, maxillary sinus, orbit, submandibular region and oral cavity can exhibit the neoplasm. Cutaneous surfaces, superficial soft tissue, lymph node, spleen or bladder are infrequently incriminated wherein histologically identical neoplasms are common [2,3].

Frequently discerned pulmonary variant with a benign clinical course is common in children and young adults. Extra-pulmonary variant is accompanied by an aggressive clinical course and incriminates individuals beyond the second decade.

Prevalence of inflammatory myofibroblastic tumour varies from 0.04% to 0.7%. Upper aero-digestive tract delineates an estimated 11% of extra-pulmonary neoplasms wherein larynx is frequently affected. Orbit, buccal mucosa and mandible are implicated wherein head and neck lesions comprise of below < 5% of extra- pulmonary sites. Oral cavity lesions are associated with an incidence of 0.0012% [2,3].

Tumour reoccurrence occurs in roughly 15% subjects. Malignant metamorphoses arises within 8% to 18% instances and distant metastasis is observed in beneath < 5% cases. Tumour mortality of extra- pulmonary neoplasms is around 4% [3,4].

Clinical features

An estimated one third subjects delineate associated symptoms such as fever, growth failure, malaise, weight loss, anaemia, thrombocytosis, polyclonal hyperglobulinemia and elevated erythrocyte sedimentation rate (ESR). Abdominal or retroperitoneal neoplasms represent as multiple, discrete masses incorporated within corresponding anatomical zones. Tumefaction can appear as an enlarged, expansible, ulcerated, firm to elastic, non tender nodule. Clinical symptoms usually dissipate following cogent surgical excision.

In addition to discernment of tumour nodule, cogent clinical symptoms are gastrointestinal complaints arising due to intra- abdominal lesions or nonspecific abdominal pain besides cough, chest pain or haemoptysis arising on account of pulmonary neoplasms [3,4].

An estimated 15% to 30% subjects are associated with constitutional syndrome denominated by fever, weight loss or malaise. The tumefaction can be discovered incidentally, associated with pyrexia of unknown origin or growth failure. As clinical representation is ambiguous, the neoplasm mandates a segregation from associated infections, granulomatous reaction, autoimmune disorders or malignant neoplasms [3,4].

Histological elucidation

Grossly, the neoplasm is firm, fleshy, gelatinous, well circumscribed, un-encapsulated and appears as a grey/white or tan coloured nodule. Tumefaction may be superimposed with atrophied, para-keratinized, stratified squamous epithelium. Cut surface is whorled, fleshy or myxoid. Foci of haemorrhage, necrosis or calcification may be denominated. Tumour magnitude varies from 1 centimetre to in excess of >20 centimetres with mean diameter of 6 centimetres [4,5].

Histologically, the variably cellular neoplasm characteristically displays proliferation of spindle-shaped cells intermixed within myxoid to collagenous stroma and prominent, inflammatory infiltrate chiefly composed of plasma cells and lymphocytes with occasional eosinophils and neutrophils [4,5].

The tumefaction is comprised of singular or admixed, distinct histological patterns denominated as •myxoid/ vascular pattern

- Compact spindle cell pattern.
- Hypo-cellular, fibrous (fibromatosis-like) pattern [2,3].
- The myxoid/vascular pattern demonstrates fasciitis-like configuration with loosely-arranged, plump, spindle-shaped cells commingled within an oedematous or myxoid stroma and accompanying prominent vasculature. Admixed inflammatory infiltrate delineates elevated neutrophils and eosinophils with minimal plasma cells [2,3].
- The compact, spindle cell pattern is characterized by proliferation of spindle-shaped cells articulating a fascicular or storiform architecture wherein tumour cells are intermingled within a collagenous stroma. Inflammatory foci are typically composed of innumerable plasma cells and lymphocytes which are intimately admixed with spindle-shaped cells. Discreet lymphoid follicles and aggregates of plasma cells are frequently observed [2,3].
- The hypo-cellular, fibromatosis-like tumour architecture is composed of elongated spindle-shaped cells intermingled within a dense, collagenous stroma with disseminated lymphocytes, plasma cells and eosinophils.

Foci of dystrophic calcification and metaplastic ossification can be exemplified within hyalinised areas [2,3].

Few neoplasms depict foamy macrophages. Foci of myxomatous degeneration are exhibited. Typically, myofibroblastic spindle-shaped cells are uniform with pale, eosinophilic cytoplasm, plump, elliptical or tapering, vesicular nuclei and miniature nucleoli. Mild nuclear pleomorphism is observed although nuclear hyperchromasia is absent [4,5].

Approximately 50% of neoplasms depict scattered, enlarged, polygonal, ganglion- like cells with abundant amphophilic or eosinophilic cytoplasm, enlarged, vesicular nuclei and prominent nucleoli [4].

Mitotic activity is minimal and appears as 0 to 2 mitosis per 10 high power fields. Atypical mitosis are exceptional. Necrosis and vascular invasion is infrequently documented [4,5].

As the neoplasm is composed of myofibroblastic and fibroblastic spindle-shaped cells intermingled with an inflammatory exudate constituted of lymphocytes, plasma cells, eosinophils or histiocytes with abundant vascular articulations intermixed with the cellular component, an admixture of distinctive articulations is enunciated

a) Tumour configuration simulating nodular fasciitis with the occurrence of elongated myofibroblasts incorporating abundant, eosinophilic cytoplasm and vesicular nuclei, a circumscribing, loose myxoid stroma with disseminated neutrophils, lymphocytes, eosinophils, and minimal plasma cells.

b) Cellular neoplasm constituted of spindle-shaped myofibroblasts and fibroblasts encompassed within a compact stroma, configuring tumour cell islands with circumscribing fibromyxoid stroma and intermingled, prominent, plasma cells. Mitotic figures can be observed.

c) Densely hyalinised stroma admixed with few spindle-shaped cells with minimal exudation of plasma cells or lymphocytes [4,5].

Ganglion-like cellular myofibroblasts may be discerned. Aforesaid tumour patterns are devoid of nuclear pleomorphism or atypical mitotic figures [4,5].

Malignant metamorphoses is associated with emergence of atypical polygonal cells with elliptical nuclei and prominent nucleoli. Reed-Sternberg- like cells or atypical mitotic figures can be discerned. Exceptionally, inflammatory myofibroblastic tumour can progress to morphologically high grade lesions. Neoplasms depict enhanced cellularity, significant nuclear atypia, frequent mitosis, atypical mitotic figures and/or tumour necrosis. High grade tumours are hyper-cellular and composed of spindle-shaped cells, epithelioid cells, histiocytoid cells or spherical tumour cells [4,5].

On ultrastructural examination, the neoplasm is predominantly composed of myofibroblasts, activated fibroblasts with minimal fibroblastic component. Ganglion-like cells demonstrate features of fibroblasts [4,5].

Molecular modifications

Genomic rearrangement of anaplastic lymphoma kinase (ALK) situated upon locus on chromosome 2p23 is documented in pulmonary and extra-pulmonary neoplasms. Aforesaid features confirms neoplastic nature of the lesion and segregates it from associated inflammatory pseudo-tumours. Anaplastic lymphoma kinase (ALK) gene encodes receptor tyrosine kinase wherein approximately 50% of neoplasms demonstrate ALK genetic rearrangements, as discerned by fluorescent in situ hybridization (FISH) [2,4].

Numerous fusion partners of ALK gene are identified within the neoplasm such as TPM3 at chromosome 1p23, TPM4 at chromosome 19p13, ATIC at chromosome 2q35, CLTC at chromosome 17q23, CARS at chromosome 11p15, RANBP2 at chromosome 2q13 and SEC31L1 at chromosome 4q21. TPM3-ALK, ATIC-ALK and CLTC-ALK fusion proteins are commonly discerned in inflammatory myofibroblastic tumour. RANBP2-ALK genetic fusion is accompanied by an aggressive, round cell transformation of the neoplasm [2,4].

Clonal anomalies of chromosome 2p23 with translocation t(2;5)(p23;q35) incriminating ALK and NPM genes is denominated. Also, chromosomal translocation t(2;17)(p23;q23) along with ALK and CLTC genes and chromosomal translocation t(2;19)(p23;p13.1) in concurrence with ALK and TPM4 genes is observed [2,4].

Majority of fibroblastic and myofibroblastic neoplasms such as nodular fasciitis, desmoid fibromatosis, calcifying fibrous tumour, myofibromatosis, infantile fibrosarcoma are devoid of anaplastic lymphoma kinase (ALK) genetic rearrangements.

However, ALK gene is enunciated within malignant peripheral nerve sheath tumour, rhabdomyosarcoma, Ewing's sarcoma, leiomyosarcoma, extraskeletal myxoid chondrosarcoma or benign and malignant adipocytic neoplasms [2,4].

Immune histochemical elucidation

Inflammatory myofibroblastic tumour is diffusely and intensely immune reactive to vimentin, focally immune reactive to α-smooth muscle actin(α-SMA) (80% to 90%), CD68, desmin and calponin (60 to70%). Approximately one third (33%) neoplasms are focally immune reactive to keratin [3,4].

An estimated 50% of neoplasms are immune reactive to anaplastic lymphoma kinase (ALK), discerned in young individuals. Immune reactivity is indicative of ALK genomic rearrangement which can be detected by fluorescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR). Pattern of ALK immune staining is concordant with specific genomic fusion. Cellular localization of ALK is determined by pertinent fusion partner with consequent diffuse cytoplasmic staining of ALK within cytoplasmic proteins TPM3, TPM4, CARS, ATIC and SEC31L1 fusion partners. Nuclear membrane staining with nuclear core protein RANBP2 fusion partner and granular, cytoplasmic staining of predominant structural protein of coated vesicles CLTC fusion partner is exemplified [2,4].

Infiltrating plasma cells are polyclonal. Inflammatory myofibroblastic tumour is immune non reactive to S100 protein, CD117, CD34, human herpes virus 8 (HHV8) and h-caldesmon [3,4].

Differential diagnosis

Histological segregation of inflammatory myofibroblastic tumour is contingent to dominant morphological pattern such as myxoid/vascular, compact spindle cell or fibromatosis-like tumour articulation.

- Spindle cell sarcoma, spindle cell melanoma or sarcomatoid carcinoma require demarcation from compact spindle cell pattern. Aforesaid neoplasms depict mild cytological atypia, predominant inflammatory infiltrate with negligible plasma cell exudate and foci of tumour necrosis, vascular invasion, hyperchromatic nuclei or atypical mitosis [2,4].

- Dedifferentiated liposarcoma, especially low grade tumour zones, appear bland on histology and are immune reactive to MDM2, akin to inflammatory myofibroblastic tumour. However, dedifferentiated liposarcoma appears in elderly population and is accompanied by adjacent areas of high grade neoplasm or well differentiated liposarcoma [2,4].

- Mesenchymal tumours of gastrointestinal tract, mesentery or gastrointestinal stromal tumour require distinction from abdominal, cellular, inflammatory myofibroblastic tumour. Uniform cellular component of gastrointestinal stromal tumour displays pale, eosinophilic, syncytial cytoplasm. Inflammatory exudate can be discerned although plasma cells are infrequent. Tumour cells are immune reactive to c-kit [2,4].

- Dendritic cell neoplasm characteristically demonstrates evenly disseminated chronic inflammatory cell infiltrate admixed with spindle-shaped cellular component. Follicular dendritic cell (FDC) sarcoma is immune reactive to CD21 and/or CD35 and interdigitating cell sarcoma is uniformly immune reactive to S100 protein. The exceptional fibroblastic reticulum cell (FBRC) neoplasm predominantly arises from lymph nodes although the tumefaction is histologically identical with a similar immune profile of variable immune reactivity to smooth muscle actin (SMA), desmin and keratin, as inflammatory myofibroblastic tumour [2,4].

- Inflammatory leiomyosarcoma is an exceptional neoplasm with a predilection for young adults. Tumour configuration is mixed storiform and fascicular spindle cell with prominent admixture of inflammatory infiltrate with innumerable foamy macrophages. Adjacent zones of typical leiomyosarcoma with fascicles of spindle-shaped cells incorporated with cigar-shaped nuclei and bright, eosinophilic cytoplasm are observed [2,4].

- Desmoid fibromatosis or calcifying fibrous tumour requires segregation from fibromatosis-like or hypo-cellular, fibrous inflammatory myofibroblastic tumour, contingent to degree of stromal hyalinization. Desmoid fibromatosis, especially mesenteric lesions, frequently denominates focal, fasciitis- like areas. Classic morphology with spindle-shaped cells demonstrate characteristic, elongated fascicles admixed with lymphocytic infiltrate with infrequent plasma cells. Desmoid fibromatosis depicts aberrant, nuclear, immune reactive β-catenin [2,4].

- Calcifying fibrous tumour is an exceptional, benign neoplasm with broad anatomical distribution. Tumefaction commonly emerges within young individuals and represents a delayed stage of inflammatory myofibroblastic tumour. Histologically, the hypo-cellular calcifying fibrous tumour denominates scattered foci of psammoma-like or dystrophic calcification. Calcifying fibrous tumour demonstrates an absence of myofibroblastic proliferation and is immune non-reactive to actin [2,4].

- Immunoglobulin G4 (IgG4) related sclerosing lesions demonstrate accumulation of immunoglobulin G4 (IgG4)- rich plasma cells. Also, proportion of plasma cells accumulating immunoglobulin G4 to immunoglobulin G (IgG4/IgG) is enhanced [3,4].

- Low grade myofibroblastic sarcoma is a cellular, infiltrative neoplasm which displays uniform appearance, prominent nuclear hyperchromasia and is immune reactive to anaplastic lymphoma kinase (ALK).

- Obstructive phlebitis delineates focal acute and chronic inflammatory exudate and an absence of anaplastic lymphoma kinase (ALK) [3,4].

- Nodular fasciitis requires segregation from myxoid/vascular variant of inflammatory myofibroblastic tumour. Nodular fasciitis appears in older subjects and rapidly enlarges over weeks or months although the miniature nodule is invariably few centimetres in magnitude. Typically, the neoplasm arises within subcutaneous tissue or skeletal muscle, demonstrates a minimalistic inflammatory infiltrate and an absence collagenous, storiform or fascicular tumour configuration [3,4].

- Reactive processes with abundant granulation tissue necessitate separation from myxoid/ vascular pattern of inflammatory myofibroblastic tumour. Cogent history and histological features of a reactive or posttraumatic process demonstrate an organized, vascular configuration with necrosis of adjacent adipose and soft tissue [3,4].

- Pseudo-sarcomatous myofibroblastic proliferations mandate a differentiation from fasciitis- like inflammatory myofibroblastic tumour arising from genitourinary tract. Pseudo-sarcomatous proliferations occur in adult subjects, are devoid of systemic symptoms or distant metastasis and exemplify localized reoccurrence in around 10% to 20% instances. Tumefaction is composed of haphazard, loose, fascicular articulation of spindle-shaped cells with elongated, bipolar, eosinophilic cytoplasmic processes. Intervening vascular stroma is typically oedematous or myxoid and imbued with variably dense, acute or chronic inflammatory exudate. Pseudo-sarcomatous proliferations may depict focal, cellular fibroblastic zones with an infrequent storiform, hypo-cellular, fibrous tumour configuration. Inflammatory infiltrate is minimal with insignificant plasma cells. Pseudo-sarcomatous proliferations are immune reactive to smooth muscle actin (SMA) (70%), desmin (35% to 60%), keratin (42% to 94%) and may be immune reactive to anaplastic lymphoma kinase (ALK) [2,4].

Additionally, the neoplasm mandates segregation from solitary fibrous tumour, benign fibrous histiocytoma, fibrosarcoma, follicular tumour, myofibroma or odontogenic tumours of mesenchymal origin such as odontogenic fibroma, odontogenic myxoma or odontogenic fibromyxoma [6].

Investigative assay

Evaluation of haematological parameters demonstrates microcytic anaemia, elevated erythrocyte sedimentation rate (ESR), thrombocytosis and polyclonal hypergammaglobulineamia. Multiple tissue samples may be required to adequately determine the condition on account of variable histological representation. Essentially a diagnosis of exclusion, tumour discernment can be confirmed with immunohistochemistry. Inaccurate diagnosis can engender aggressive surgical intervention or radical resection with subsequent functional disability [6,7].

Therapeutic options

Cogent treatment strategies are steroid therapy, surgical resection, curettage, radical therapy, singular radiotherapy or in combination with aforesaid therapeutic manoeuvers. Treatment options are selected contingent to clinical history, tumour localization, tumour reoccurrence, extent and biological behaviour [6,7].

Optimal treatment modality is comprehensive surgical eradication of the neoplasm. The neoplasm is amenable to comprehensive surgical extermination. Marginal resection with excision of a broad, tumour-free perimeter can be suitably adopted. Tumour associated systemic manifestations generally resolve with adequate surgical extermination of the neoplasm [6,7].

Although a frequently employed treatment modality, surgical excision can be supplemented with carbon dioxide (CO_2) laser technique. Steroids, radiation therapy and chemotherapy with agents such as cyclosporine, azathioprine, methotrexate, cyclophosphamide or

molecular, ALK targeted agents such as crizotinib can be adopted for managing invasive, reoccurring, malignant, metastatic neoplasms unamenable to surgical resection or tumefaction with infiltrated tumour-perimeter [7,8].

Tumour reoccurrence pertains to anatomical site and varies from below < 2% for pulmonary neoplasms to around 25% to 35% for extra- pulmonary neoplasms. Tumour relapse is common with multinodular, intra-abdominal tumefaction and neoplasms arising within delicate anatomical locations as larynx or trachea which may be unamenable to comprehensive surgical extermination. Tumour relapse following competent, adequate tumour eradication of a solitary neoplasm is extremely exceptional. Tumour reoccurrence is indicated by reappearance of aberrant clinical and haematological manifestations [8,9].

Distant metastasis is exceptional and is discerned in beneath < 5% instances. Frequent sites of distant metastasis are pulmonary parenchyma, brain, hepatic parenchyma or bone. Metastatic manifestations are discernible at initial presentation or within a year although can appear up to 9 years following surgery [8,9].

Features such as tumour magnitude, cellularity, mitotic activity, nuclear atypia, ganglion-like cells and tumour necrosis lack concurrence with tumour aggressiveness and prognostic outcomes. An estimated 50% of metastatic neoplasms are devoid of atypical morphological manifestations [8,9].

Prognostic outcomes are inferior, especially in neoplasms arising within abdominal or pelvic sites. Tumours which are immune nonreactive to ALK are associated with unfavourable prognosis. Exemplification of ALK genomic rearrangement and disease prognosis or tumour reoccurrence lack concurrence. Neoplasms depicting ALK immune reactivity display minimal possibility of distant metastasis. Similarly, p53 is enunciated in around < 10% to 80% neoplasms and lacks concordance with tumour aggressiveness [8,9].

Flow cytometric analysis of DNA aneuploidy may be concordant with enhanced possibility of tumour reoccurrence [8,9].

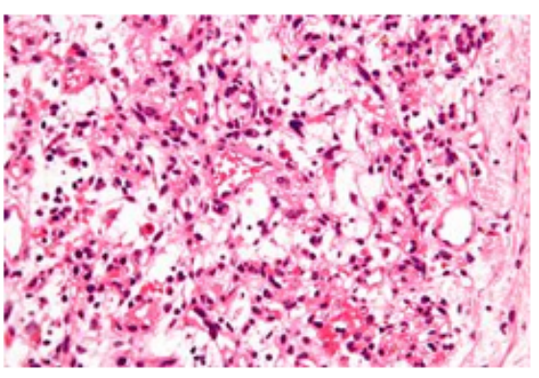

Figure 1: *Inflammatory myofibroblastic tumour delineating fascicles of spindle-shaped cells intermixed with lymphocytes, macrophages, plasma cells and an encompassing fibro-connective tissue stroma [10].*

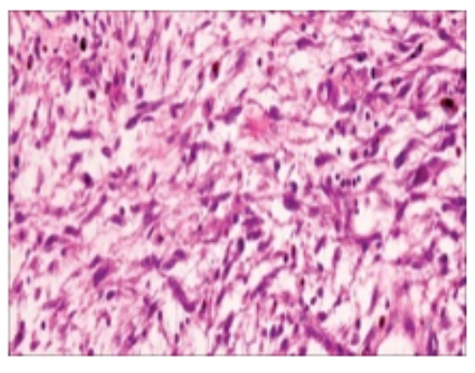

Figure 2: *Inflammatory myofibroblastic tumour depicting fascicles of spindle-shaped cells admixed with a chronic inflammatory exudate and absence of atypia [11].*

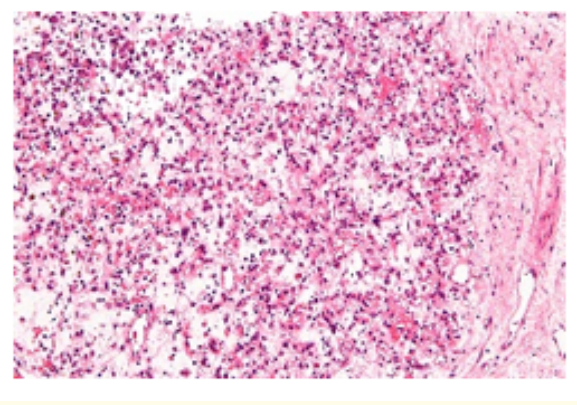

Figure 3: *Inflammatory myofibroblastic tumour depicting fibroblastic and myofibroblastic cells commingled with inflammatory infiltrate of lymphocytes, plasma cells, eosinophils, enmeshed within a collagenous stroma [12].*

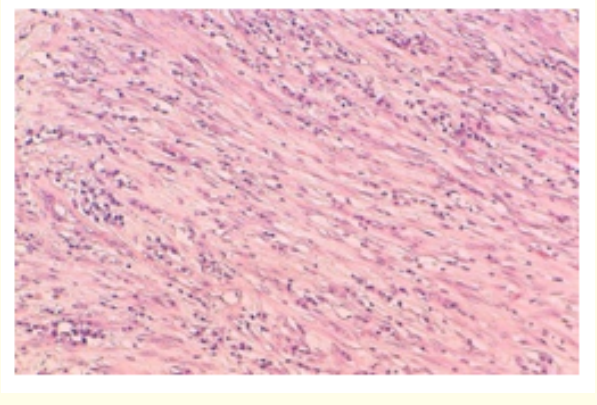

Figure 4: *Inflammatory myofibroblastic tumour exhibiting bundles of spindle-shaped cells with interspersed chronic inflammatory cells, plasma cells and an enveloping collagenous stroma [13].*

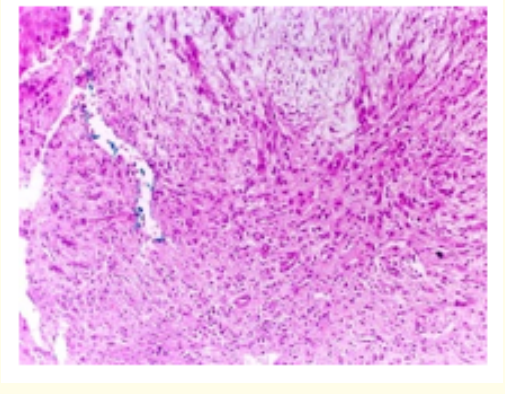

Figure 5: *Inflammatory myofibroblalstic tumour demonstrating fascicles of spindle-shaped cells intermixed within a chronic inflammatory infiltrate, plasma cells and collagenous stroma [14].*

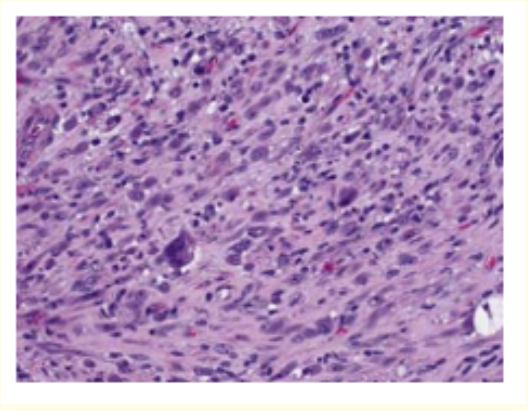

Figure 6: *Inflammatory myofibroblastic tumour enunciating bundles of fibroblastic and myofibroblastic cells dispersed within a chronic inflammatory cell exudate and collagen tissue fragments [15].*

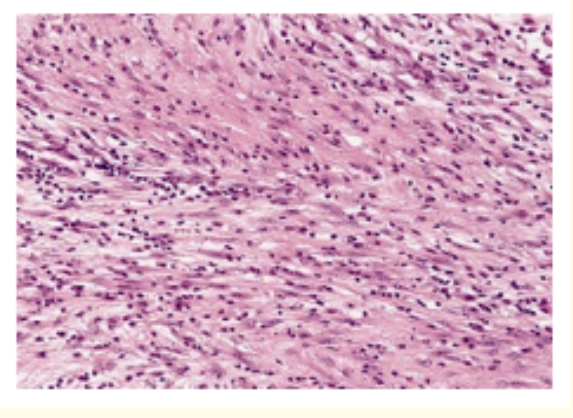

Figure 7: *Inflammatory myofibroblastic tumour delineating fascicles of spindle shaped cells admixed with chronic inflammatory cells and several plasma cells disseminated within a collagenous stroma [16].*

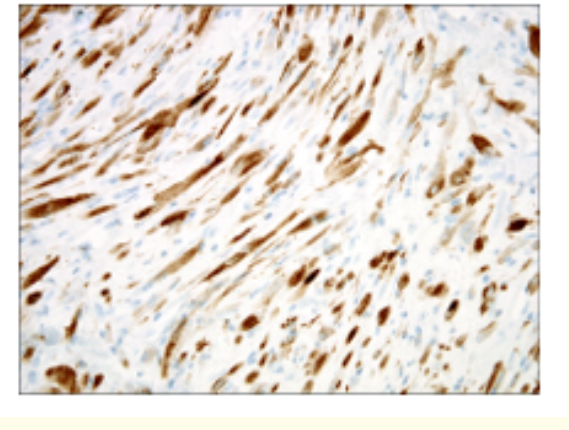

Figure 8: *Inflammatory myofibroblastic tumour immune reactive to ALK [17].*

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12. Image 3 Courtesy: Wikipedia.com.

13. Image 4 Courtesy: Diagnostic pathology.

14. Image 5 Courtesy: eScholarship.com.

15. Image 6 Courtesy: Doctor Lib Info.

16. Image 7 Courtesy: Pathology outlines.

17. Image 8 Courtesy: Journal of Clinical Pathology.

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