# Inflammatory myofibroblastic tumor

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## Abstract

Inflammatory myofibroblastic tumor is an uncommon lesion of unknown cause. It encompasses a spectrum of myofibroblastic proliferation along with varying amount of inflammatory infiltrate. A number of terms have been applied to the lesion, namely, inflammatory pseudotumor, fibrous xanthoma, plasma cell granuloma, pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, inflammatory myofibrohistiocytic proliferation, benign myofibroblatoma, and most recently, inflammatory myofibroblastic tumor. The diverse nomenclature is mostly descriptive and reflects the uncertainty regarding true biologic nature of these lesions. Recently, the concept of this lesion being reactive has been challenged based on the clinical demonstration of recurrences and metastasis and cytogenetic evidence of acquired clonal chromosomal abnormalities. We hereby report a case of inflammatory pseudotumor and review its inflammatory versus neoplastic behavior.

**Keywords:** ALK-1, myofibroblasts, neoplastic, reactive

## Introduction

Inflammatory myofibroblastic tumor (IMT) is an uncommon lesion of unknown cause. It encompasses a spectrum of myofibroblastic proliferation along with varying amount of inflammatory infiltrate. A number of terms have been applied to the lesion, namely, inflammatory pseudotumor, fibrous xanthoma, plasma cell granuloma, pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, inflammatory myofibrohistiocytic proliferation, benign myofibroblatoma, and most recently, inflammatory myofibroblastic tumor. The diverse nomenclature is mostly descriptive and reflects the uncertainty regarding its true biologic nature of these lesions.[1]

IMT was first observed in lungs and described by Bunn in 1939. It was named as IMT by Umiker *et al*. because it mimics malignant neoplasm clinically, radiologically and histopathologically. Various pathogenetic backgrounds have been proposed as initiating factors such as reactive, infections, autoimmune and neoplastic processes, but the etiology of most remains unknown. Recently, the concept of this lesion being reactive has been challenged based on the clinical demonstration of recurrences and metastasis and cytogenetic evidence of acquired clonal chromosomal abnormalities.[1,2] The lungs, liver and gastrointestinal tract (GIT) are the most common sites for IMT. In the head and neck, it has been reported in epiglottis, endolarynx, parapharyngeal spaces, maxillary sinus, submandibular region and oral cavity.[3]

IMT in the maxillofacial region is exceptionally rare, and it is often mistaken as malignancy. The diagnosis is still difficult and based on the histologic examination of the lesions.[4] In the oral cavity, IMTs have been reported in multiple locations like gingiva, tongue, hard palate, mandible, buccal mucosa and submandibular salivary gland.[5,6]

Clinically, they are painless, indurated mass or swelling of relatively short duration or following specific symptoms related to the site of origin. They have no age preferences, but the affected patients tend to be children and young adults.[7]

Computed tomography (CT) scan and magnetic resonance imaging (MRI) of IMTs in the head and neck region might be nonspecific and often suggest infiltrative growth, aggressive malignant lesion or granulomatous disease.[7]

IMTs of head and neck are generally benign lesions and usually cured by radical excision, steroids, irradiation and/or chemotherapy. CO2 laser is a new modality of treatment.[7]

## Case Report

A 19-year-old male patient reported to Sinhgad Dental College and Hospital (SDCH) with a complaint of swelling over right side of face since 3 months. On examination, diffuse extraoral swelling was found on right side of the face [Figure 1]. The swelling was firm on palpation, overlying skin was normal and it was mildly tender in nature. Intraoral examination revealed an oval mobile swelling extending from 44 region to the

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angle of the mandible in the buccal vestibule, which was non-tender and not fixed, and the overlying mucosa was normal. Incisional biopsy was taken and the H and E stained section showed non-encapsulated mass composed of connective tissue stroma with diffuse and focal infiltration of lymphocytes, plasma cells and histiocytes. Focal areas of inflammatory cells were seen gathered around blood vessels and also forming germinal centers. Spindle-shaped cells were seen interspersed in the connective tissue [Figure 2a and b]. Based on the findings, a diagnosis of IMT was rendered. The lesion was surgically excised and subjected to immunohistochemical staining which showed strong vimentin positivity [Figure 3a and b], smooth muscle actin (SMA) positivity in spindle cells [Figure 3c] and focal positivity for Anaplastic Lymphoma Kinase ALK-1 [Figure 3d] in the spindle cells. The diagnosis of IMT (lymphoplasmacytic variant) was confirmed.

## Discussion

Lymphocytes, plasma cells, histiocytes, fibroblasts and myofibroblasts are the basic components of IMT, present in variable proportions. Four basic histologic patterns are commonly seen as follows:

a. Dominant lymphoplasmacytic infiltrate;
b. Dominant lymphohistiocytic infiltrate;
c. Young and active myofibroblastic process and
d. Predominantly collagenized process with lymphocytic infiltrate.

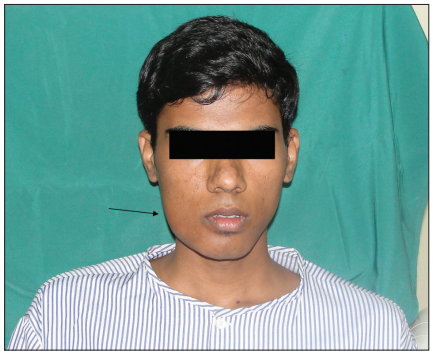

**Figure 1:** Pre-operative photograph showing diffuse extraoral swelling

The lymphoplasmacytic IMT consists of a mature lymphoid and plasma cell infiltrate with germinal centers, hence the name given is plasma cell granuloma.[3]

Lymphohistiocytic IMT most commonly resembles an infectious process as foamy histiocytes are predominant.[3]

The young and active IMT has a densely cellular fascicular and storiform pattern resembling fibrous histiocytoma except for the inflammatory infiltrate or nodular fascitis.[3]

Collagenized IMT is less cellular and resembles a desmoid tumor but with a prominent inflammatory infiltrate. A zonation/maturation effect may be observed. Progression of patterns may also be seen in some longstanding cases, necessitating multiple procedures.[3]

Recently, the concept of IMT being a benign reactive lesion has been challenged owing to clinical demonstration of recurrences as high as 37%, the presence of regional metastases and cytogenetic evidence of acquired clonal chromosomal abnormality. However, the issue of reactive versus neoplastic pathogenesis of this lesion remains unsolved.[7]

There are cases of IMT that clinically and radiologically

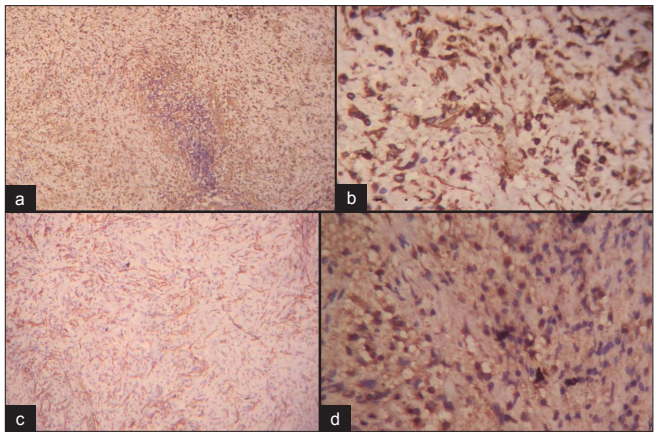


**Figure 3:** (a) Focal ALK-1 positivity seen in spindle cells (×100); (b) SMA positivity seen in spindle cells (×100); (c) vimentin positivity in spindle cells (×100); (d) vimentin positivity seen in spindle cells (×400)

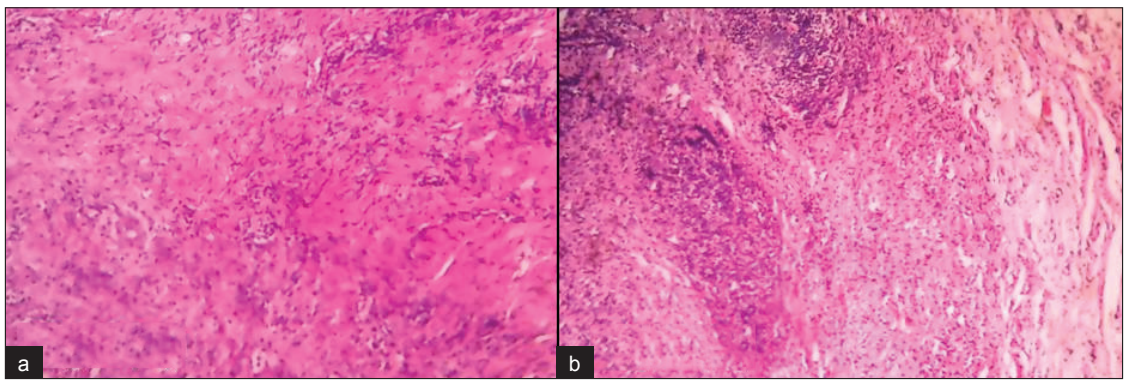


**Figure 2:** (a) Spindle cell proliferation (×100); (b) inflammatory cells forming germinal centers (×100)

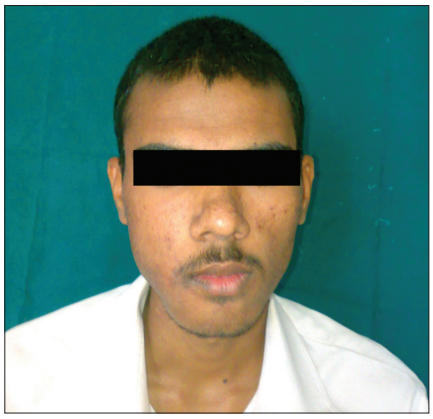

**Figure 4:** Postoperative photograph

may simulate malignant tumors, but the bland histologic appearance of proliferating spindle cell and plasma cell rich inflammatory background is characteristic. Cellularity, mitotic counts and extent of inflammation do not appear to be prognostic. In contrast, some authors state that at least a subset of IMTs represent true neoplasm and found that cytological atypias, presence of ganglion like cells, p53 expression and DNA aneuploidy may be useful for identifying tumors that are more likely to pursue an aggressive clinical behavior with recurrences and malignant transformation.[7]

The neoplastic behavior is reflected by some cytogenetic and immunofluoroscence aberrations, especially chromosome 2p23 involving the Anaplastic Lymphoma Tyrosine Kinase (ALK) receptor and its fusion with clathrin heavy chains.[8] This abnormality has been detected in up to 50% of soft tissue IMTs. Other abnormalities in t(2, 17), (p23, q23), tropomyosin 4 (TPM 4), TPM 3, t(p25, p23), cysteinyl tRNA synthetase and Ran binding protein also have been identified in IMTs. It appears that ALK-1 expression is highly specific for IMT, but it is not 100% sensitive, depending to some extent on the site of origin. ALK-1 negative IMTs are morphologically indistinguishable from ALK-1 positive cases. No clinical, morphological or prognostic difference is found associated with ALK-1 status of the IMT. Nodular fascitis and desmoid fibromatoses do not express ALK-1.[7,9]

Cytogenetic and molecular studies point to the possibility that some subsets of IMTs are in fact true monoclonal neoplasms, and are also invasive and locally recurrent. Metastatic forms of abdominal, mediastinal and paranasal sinus IMTs have also been reported. In contrast to the latter, there are others who believe that the reported cases are multicentric IMTs and not a true metastasis.[9]

It is suggested that inflammatory mediators such as cytokines and interleukin-1 (IL-1) are released in response to an insult causing proliferation of fibroblasts, leaky and pro-coagulant endothelium and extravasation of polymorphous cellular infiltrate into the extracellular spaces.[4] Several triggers for its development have been described, including smoking, minor trauma, post-adenoidectomy and infection; however, the exact etiology is not known [Figure 4].[1,3]

Some cases have been reported as having bacterial etiology and Epstein–Barr virus (EBV). Few large pathological series exist, but there is no apparent age, ethnic or geographic predilection.[1,2] The list of infectious agents is expanding, such as *Mycobacterium*, actinomycetes, *Nocardia*, mycoplasm, *Escherichia coli*, *Klebsiella*, *Bacillus sphaericus*, *Pseudomonas*, HIV, *Helicobacter pyroli*, EBV, human herpes virus 8 (HHV-8).[7,9,10]

The D/D of IMT comprises low-grade myofibroblastic sarcoma as well as a long list of benign, reactive or neoplastic spindle cell lesions, such as leiomyoma, solitary fibrous tumor, spindle cell carcinoma, nodular fascitis and peripheral nerve sheath tumor.[2]

Mitotic figures and plump spindle cells are present, but nuclear pleomorphism and apoptosis are not usually seen in IMT. Their presence should lead one to consider an inflammatory sarcomatous process or spindle cell carcinoma. IMT may overlap, in terms of biologic potential and histology, with the entity described as a "low-grade inflammatory fibrosarcoma." The plasmacytic and histiocytic component of IMT may raise the possibility of infections such as syphilis and atypical mycobacterium. In such cases, special stains (acid fast bacillus, silver stain) are warranted. Autoimmune diseases (lupus erythematosus, rheumatoid arthritis) can cause intense laryngeal inflammation, and hence appear as an inflammatory pseudotumor.[2]

The diagnosis of nodular fascitis, fibrous histiocytoma and fibromatosis can come to the mind when examining IMT. Perhaps IMT is also related to these processes, but features like storiform pattern, lack of necrosis, and pronounced chronic inflammatory component are inconsistent with those processes. Overlapping histologic features between IMT, nodular fascitis and fibrous histiocytoma corroborate the place of these entities in the pathologic spectrum between reactive and neoplastic process.[2]

In IMTs, spindle cells lack the cytologic atypia and nuclear hyperchromasia of sarcomas. The immunohistochemistry is usually utilized to confirm the myofibroblastic phenotype of the tumor spindle cells which are typically reactive to vimentin (99%), SMA (92%), muscle-specific actin (89%), and desmin (69%). Spindle cells may be focally positive to epithelial markers such as cytokeratin, epithelial membrane antigen (EMA; 36%) and CD68 (25%). IMTs are typically negative for myoglobin and S100 protein. Only few splenic and liver IMTs, particularly those in immunosuppressed patients, were found to be positive to EBV-latent membrane protein (LMP) and HHV-8.[7,9] IL-6 promotes proliferation of fibroblasts, and both IL-1 and IL-6 promote differentiation of B cells. Major cellular sources of IL-1 and IL-6 are monocytes and macrophages which are constant constituents of IMT.[11]

It is quite common for patients with IMT to undergo multiple biopsy procedures to establish a diagnosis. On biopsy evaluation, IMT appears to be a diagnosis of exclusion. The polymorphous appearance of IMT reflects its variable etiology or its shifting histology during the course of the disease.[7,12]

In general, IMT follows benign course with favorable outcome after radical local excision.However, invasive, locally recurrent and metastatic forms have been reported in abdomen, mediastinum and paranasal sinuses..[7,12]

## Conclusion

In our case, there was a strong positivity of vimentin and SMA in the spindle-shaped cells, while a focal faint positivity of ALK-1 was seen. Moreover, the absence of cytological atypia and nuclear hyperchromasia in the spindle-shaped cells prompted the diagnosis of IMT (lymphoplasmacytic variant). The lesion was surgically excised and there was no sign of recurrence after 6 months of follow-up.

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