Inflammatory Myofibroblastic Tumor in the Maxillary Sinus – an Extremely Rare Entity
SM Dissanayake, WRAPP Rajapaksha

Abstract
Inflammatory Myofibroblastic Tumor (IMT) is a rare spindle cell neoplasm of contentious etiopathology. IMT carries a diverse nomenclature with a predilection for children and young adults.

The common sites are the lungs and abdominopelvic region, and its biologic behavior remains unpredictable. IMT in the maxillofacial region is extremely rare.

Diagnosis of IMT is by histopathology. Immunohistochemistry is utilized for differentiation and confirmation as it shares many features of other spindle cell neoplasms. Various treatment modalities have been practiced and its response to anti-inflammatory agents is fascinating. Local recurrence is almost encountered in cases managed by surgery. Close follow up is crucial.

We report a case of IMT in a 48 year old female that was initially non-resectable and showed improvement to anti-inflammatory medication.

Key words: Inflammatory myofibroblastic tumor, anti-inflammatory drugs, recurrence

Introduction
Inflammatory Myofibroblastic Tumor (IMT) is a rarer neoplastic entity with a multitude of characteristics. It was first described by Brunn in 1939, as a tumor with both neoplastic and non-neoplastic features. A spectrum of lesions were addressed by the umbrella term “Inflammatory pseudo tumor” until the term IMT was coined by Umiker and Iversion. Beforehand, a diverse nomenclature has been applied such as fibrous xanthoma, plasma cell granuloma, benign myofibroblastoma and inflammatory myofibroblastic proliferation.

IMT is a benign neoplasm of great controversy. In the surgical pathology criteria published by Stanford University, IMT is defined as a “tumor composed of cytologically bland, spindled myofibroblasts with admixed inflammatory cells, predominantly occurring in infants and children”.

The chance of encountering an IMT is very rare and occurrence in the maxillofacial region is exceptionally rarer.

Usual victims organs are lungs and bladder. In the maxillofacial region, epiglottis, para pharyngeal spaces, maxillary sinus, gingivae, tongue and buccal mucosa have been reported.

Symptoms of IMT are attributable to site and the extent of the lesion. Generally, these are painless but enlarge with induration. The diagnosis of IMTs extremely challenging due to the vast clinical and histological variance owing to both neoplastic and inflammatory characteristics.

Dr S. M. Dissanayake (Correspondence), Registrar in OMF Surgery, Colombo North Teaching Hospital, Ragama. 0773847381, E mail-madhubhani.dissanayake@gmail.com
Dr. W.R.A.P.P. Rajapaksha Consultant Oral & Maxillofacial Surgeon, Colombo North Teaching Hospital, Ragama
Inflammatory Myofibroblastic Tumor in the Maxillary Sinus – an Extremely

Even though excision has been practiced to fulfill both therapeutic and diagnostic goals, there is no universally accepted treatment protocol to date.\textsuperscript{10} Corticosteroids, Non-Steroidal Anti-Inflammatory Drugs [NSAID] and other chemotherapeutic agents have demonstrated rewarding improvement in non-resectable IMTs.\textsuperscript{2,6} Loco-regional recurrences and metastasis involving multiple foci are worrisome in IMTs.\textsuperscript{1,2,6}

In the following case, a rare occurrence of an extensive, non-resectable IMT in the right maxillary sinus of a 48 year old lady, treated with a simple anti-inflammatory regimen is narrated.

Case report

A 48 year old lady from Chilaw presented to Oral & Maxillo Facial Unit [OMFU], Colombo North Teaching Hospital [CNTH], Ragama, complaining of a dull ache on the right jaw for five months and a swelling on right cheek for four months. [Figure 01& 02] She has initially experienced a mild throbbing, poorly localized pain in upper right jaw, which has gradually increased in severity. The pain was radiating to right ear, temporal, frontal, mastoid regions. Its’ onset was spontaneous and partially relieving for paracetamol. She has not felt any sensory disturbance over the face on theright compared tothe left side.

Since she has perceived it as a “toothache”, she had seen a general dentist and undergone extraction of a carious tooth without any resultant relief of pain. The extraction socket has healed uneventfully. Yet, approximately after a month, a swelling had appeared on her right cheek which enlarged gradually. Furthermore, she has neither experienced any kind of a discharge nor a sensory disturbance in relation to the swelling.

She had undergone a total hip replacement and also was also hypertensive but attained good control with drugs.

This lady was a widow living with two daughters. She was negative for habits like chewing betel, areca or smokeless tobacco.

On examination, she looked distressed. The swelling on her right cheek was 5x5 cm with diffused borders extending over the maxilla without any changes of the surface skin. Her mouth opening was satisfactory. The mucosa covering the right alveolus appeared normal.

The facial swelling was firm in consistency with a mild tenderness elicited on palpation. The overlying facial skin was not attached to the lesion. An indurated lesion was palpated along the buccal sulcus. No cervical or other regional lymphadenopathy was detected.

An occipito-mental radiograph was requested and it revealed a diffuse radio-opacity in the right maxillary sinus. [Figure 03] Ultra sound scanning demonstrated normal parotid and submandibular glands and it confirmed the absence of cervical lymphadenopathy.

Hematological investigations revealed elevated neutrophil and eosinophil counts, erythrocyte sedimentation rate and C-reactive protein levels despite negative Mantoux test with a non-significant chest radiograph. [Figure 04]

On the above basic findings, the possibility of a neoplasm, fungal or parasitic infection was raised.

Contrast Enhanced Computed Tomogram [CECT] showed the lesion in antrum eroding the anterior wall. There was no direct extension to the brain or neck.[Figure 05]

As per the specialist microbiology opinion, multiple tissue samples were retrieved under local anesthesia with the necessary precautions. The surgical pathology report stated the presence of multiple cell types with centers failing to give a conclusion. Moreover, both the consultant
pathologist and microbiologist excluded any kind of an infection. Therefore, thorough explanation of the quandary and the procedure was made to the patient to obtain informed written consent and nextan excision was planned.

Patient was optimized as per the advice given by relevant consultants and anesthetized. Right buccal sulcus was infiltrated with 2% Lignocaine and 1:80,000 Adrenaline. An incision along the buccal sulcus was placed. A multinodular, fragile mass with gelatinous consistency was noted. It was very delicate and bled easily suggesting an enriched vascularity. Thus, it could not be excised en-bloc without unavoidable tumor fragmentation. The tumor was merging into surrounding tissues rendering the delineation of healthy tissue very difficult. The tumor was infiltrating the masseter, temporalis, medial pterygoid muscles with temporal and infra temporal fossae. Closure of the site was obtained with 3/0 Black silk. Specimens were sent to the Department of Oral Pathology, Faculty of Dental Sciences.

**Histopathology report**

The specimen was composed of spindle cells with elongated nuclei that are diffusely arranged and showing bland morphology. A dense inflammatory cell infiltrate of lymphocytes and plasma cells was evident among tumor cells; also germinal centers were noticed occasionally. [Figure 06]

Immunohistochemistry performed on the specimens have been stained positively for smooth muscle actin. [Figure 07] The supplementary report to the main histology report stated that bone pieces also show tumor deposits. [Figure 08] None of the margins were tumor free as were obvious during the surgery as well. The above histological features were consistent with those of IMT.

The controversy regarding the management and seemingly possible cure with surgical resection of the tumor was explained to the patient. Yet, she was not happy to undergo further surgeries despite the emphasis on positive tumor resection margins.

Following a discussion with the consultant oncologist, patient was enrolled for medical management with Steroids [Glucocorticoids] and Coxibs; i.e. Prednisolone 5mg and Celecoxib 100mg daily. A reassessment protocol drafted by the collaboration of specialists of visiting the clinic every month and radiographs every six months was made to appraise the response to treatment.

The need for sequential radiographic evaluation to assess the response to treatment was reiterated to the patient. Despite the gross refusal to undergo surgery under general anesthesia, she was a highly compliant patient attending all the review appointments.

After 6 months, the patient was almost symptom free even though there was CT evidence of the residual lesion in the right maxillary antrum.

After 1 year, tumor-specific symptoms were completely alleviated and the lesion on the CT seemed to be improving. [Figure 09] As per the evidence, radiographic evidence was sluggish to follow the symptomatic improvement consultant oncologist advised to continue the same regimen for another year. The patient is now totally symptom free and awaiting confirmation via radiology and histology reports.

**Discussion**

The caption “IMT” encompasses a multitude of spindle cell pathologies which traverses the clinical and histologic properties from reactive non-neoplastic lesions to encroaching malignant neoplasms.12

IMTs’ idiosyncrasies in pathophysiology, clinical behavior, therapeutic options and responses are litigious yet fascinating. Based on these grounds,
it has garnered the interest of almost all the surgical and medical specialties dealing with neoplasia.10

Due to the extreme rarity of this tumor, the entire scenario from presentation and diagnosis to treatment poses formidable challenges for clinicians. Frequently, the diagnosis is overlooked.

Although the current acceptance of the exact inducement to develop IMT remains a mystery, a few etiological agents have been considered in literature.14 Viruses, trauma, smoking, surgery and foreign bodies were conventionally assumed to cause IMT through an exaggerated immune reaction.7,11,14

There is a dichotomy regarding etiopathogenesis; traditional one proposing a reactive response and novel dogma challenging the former supporting a neoplastic process.12,11,12 On the grounds of its characteristics like, recurrence, extensive loco-regional infiltration, metastasis and malignant transformation, the latter school of thought is supported clinically.15 It is further promoted by the aberrations in the anaplastic lymphoma tyrosine kinase [ALK] receptor locus on chromosome 2p23, which is noted in approximately 50% of IMTs as reported by Tothova and the team.16 Whatsoever, the exact originator of the IMT is yet to be elucidated and majority of proponents believe the incitement is heterogeneous and attributed to both reactive and chromosomal peculiarities.17

IMT, being predominantly a visceral tumor, quite exceptionally affects the structures in the head and neck, a numerical expression accounting for less than 5% of all IMTs.12 Tragically, IMTs occurring in the maxillofacial region tend to be of heightened invasiveness and aggressive neoplastic activity.1,10 Many cases reported involve or are in close vicinity of the para nasal sinuses, exemplifying its potential to grow occupying tissue spaces.1,2,6 Also, their rate of enlargement tends to be depressingly brisk.12 In this case also the lesion was occupying the right maxillary sinus, invading the antral space and typically exhibiting a shorter duration of four months.

There have been less than five cases of IMTs originating in relation to the extraction sockets in medical literature in English.19 There is a slight hesitation to relate this case to the aforementioned category as the pain was preceded prior to the extraction and virtually mimicked odontalgia.

Clinical presentation of IMT is tremendously variable.12 Despite the marvelous developments in imaging techniques, essential features particular to IMTs have not been cited to date.15 Thus far, the necessity of imaging in terms of delineating critical anatomical architecture, especially with IMTs’ enhanced encroaching properties, cannot be overlooked. In our case, the invasion of anterior wall of the sinus by means of erosion was obvious.

Elevation of C-reactive protein and erythrocyte sedimentation rate is highlighted in almost all the cases.2,10,14 Mild leukocytosis has been exhibited as a common element in whole blood analysis.2,6,14 The non-specificity of such comprehensive findings may mislead the clinician when entertaining differential diagnoses, perhaps bringing up fortuitous impediments to commence definitive management. In our patient, there was mild eosinophilia; hence raising the possibility of a parasitic infection during drafting differential diagnoses is justified.

Definitive diagnosis of IMT is purely by histology of excised lesions.1,15 Pre-operative diagnosis is exceptionally intricate both due to its rarity and dilemmatic presentation.19 Myofibroblastic spindle cells accompanied by inflammatory cells is the fundamental prerequisite for the histological confirmation of IMT.5,13 Lymphocytes, plasma cells, fibroblasts and myofibroblasts are the
elementary cellular components of IMT.1 Bland histologic appearance in proliferating spindle cells within a plasma cell enriched inflammatory cellular stromal surrounding is peculiar to IMTs. In contradiction, some declare that the presence of cellular atypia, p53 expression along with DNA aneuploidy should ring alarm bells in clinicians’ mind indicating destructive behavior.9

The list of histological differential diagnoses IMT comprises the follicular dendritic cell tumor, low-grade myofibroblastic sarcoma, solitary fibrous tumor, leiomyoma and peripheral nerve sheath tumor.2,6

Four primary histologic patterns of IMTs have been observed as follows.1
1) Dominant lymphoplasmacytic infiltrate
2) Dominant lymphohistiocytic infiltrate
3) Young and active myofibroblastic process
4) Predominantly collagenized process with lymphocytic infiltrate

But, after the extensive work, done by Coffin and co-workers on the stroma of IMT three stromal types have been identified as myxoid, collagenized and vascularized.20 In this case, the histopathology report has clearly stated almost all the features established in literature to aid diagnosis.

So far, several cytological markers have been discovered to be secreted by IMTs.2 Desmin, smooth muscle actin, vimentin, cytokeratin, and ALK-1 are a few of these whose positivity may facilitate the diagnosis of IMT.1,2

IMTs show absolute negativity for myoglobin and S100 protein.1,20,21 In our case, none of the markers were able to exhibit their positivity for immunohistochemistry but (except for ??? check) smooth muscle actin.

Apart from physical causes, an assumptive series of agents involved in the infectious process have been published including Epstein-Barr virus, Escherichia coli, Mycobacterium, Pseudomonas, Human Immunodeficiency virus, Human Herpes virus and actinomycetes.9,21

The huge controversy over IMT being a neoplasm versus an exaggerated immune/inflammatory response, a wide variety of treatment options have been practiced by the clinicians so far.14 Up to date, there is no unequivocal consensus regarding the management of IMT established to the best of authors’ knowledge. By virtue, surgeons have always favored the resection if the lesion is resectable while oncologists favor medical management as the first line attempt.2,6,10,14

Majority of articles suggest that surgery is the mainstay of treatment and usually it is fulfilled by the pathologists’ suggestion for excision even prior to the arrival of a definitive diagnosis.10 Alleviation of all symptoms can be obtained by complete resection.10 In spite of the anticipated success, failure to amputate the absolute tumor may exert detrimental effects on the residual lesion inducing invasion of adjacent viscera and an accelerated rate of growth of the IMTs.23 Rewardingly, radical surgery has proven to be a complete cure in 90% of the cases.20,21 Yan and the team has reported a case of a flourish in IMT in the vocal cords, which was removed utilizing potassium titanyl phosphate [KTP] laser in China.15

Meanwhile, conglomerate medical therapeutic modalities including corticosteroids, NSAIDs, Cyclo-oxygenase [COX] inhibitors, kinase inhibitors along with radiotherapy and chemotherapy have been administered alone or in variable combinations with impressive outcomes.2,6,15 Non-surgical regimens breeze in when the tumor is identified and pronounced as “irresectable” and the accuracy of this critical decision is fueled by the experience of all the experts involved in the management of the patient.
Inflammatory Myofibroblastic Tumor in the Maxillary Sinus – an Extremely

Hansen in his review, reports triumphant cure of an IMT by Crizotinib an ALK-1 inhibitor prescribed in light of ALK positivity in immunohistochemistry, expecting the suppression and regression of scattered maturation zones. The response to steroids and COX inhibitors have been highlighted as fascinating by oncologists, which reflects the critical role played by the inflammatory mediators in the propagation of these tumors. In the recent literature, many clinicians have demonstrated a positive outcome for this particular tumor by administering NSAIDs while offering a reasonably conservative mode of treatment.

Even though Firat et al report that chemotherapy and radiotherapy to prove scanty improvement, Navinan and crew from Sri Lanka has published an initially inoperable IMT in the paranasal sinuses treated with methotrexate yielding extraordinary outcomes. Chemotherapy has been recommended for refractory, multifocal and invasive lesions and usually executed with methotrexate, cisplatin, vinorelbine, carboplatin, paclitaxel and Adriamycin. Documents on radiotherapy are also disputable regarding the consequences. While a few clinicians purport its’ futility in management of IMTs, considerable resolution of a naso-maxillary IMT following intensity modulated radiation therapy (IMRT) has been reported challenging the former dogma. Furthermore, more remunerative aftereffects have been entertained when radiotherapy has been combined with chemotherapy or other measures. Fortunately, when it comes to extensive, therapy resistant, recurrent lesions, neoadjuvant radiotherapy in higher doses has demonstrated beneficial results.

Modernistic therapeutic alternatives like immunoglobulins have manifested promising outcomes in curing residual lesions following excision, with long term remission.

Whatsoever, many authors have agreed that individualized multimodal therapeutic protocols are far superior in attaining cure than any variant of a monotherapy.

In this subject, even though it had taken quite a longer duration, the outcome by two simple groups of drugs has been gratifying over the massive resection patient was to undergo probably with a reconstructive option which invariably accompanies a donor site morbidity. Lesions with smaller dimensions and approachable anatomical locations that ensure the ability of complete resection with tumor free margins invariably poses optimistic bestowals on prognostication. The impact of various cellular markers on adversity of tumor propagation is a matter of current interest where investigators have been extensively working on and the positivity of ALK-1 lights up the possibility of specific administration of ALK-1 inhibitors. Howbeit, cellularity, number of mitotic figures and the degree of inflammation encountered during histological evaluation, have not been highlighted and considered to be of any prognostic value.

Local recurrence of IMT following resection has been reported to range from 25% to 37% for extra pulmonary tumors. Unfortunately, a figure as high as 85% is noted as a recurrence rate for abdomino pelvic lesions. Providentially, the rate of distant metastases remain at a very low value of less than 5%.

Behranwala recommends a long term follow up since, recurrences after many years of apparent complete regression. In spite of prudent therapeutic intervention, Brooks has endorsed a minimal mandatory follow up period of 10 years to affirm absolute cure with neither recurrences nor metastases.
Finally, almost all the authors\(^1,2,6-15\) have emphasized the paramountcy of concerted sailing in a voyage of discovery from diagnosis to sequel of cure of this fascinating entity with the inclusion of surgical, radiological, pathological, oncological and other specialties which will unfailingly lead the team to overcome diagnostic dilemmas and to opt the best responding, personalized therapeutic regimen.

**Conclusion**

IMTs are a group of benign spindle cell tumors that show overlaps in clinical behavior, terminology, radiology, histology and immunohistochemistry with many other benign and malignant pathological entities. With this degree of confusion it has posed an immense challenge to all the specialties involved in its management. The dichotomy pertaining to its etiology i.e. neoplastic and inflammatory/immunological origin has linked many strategies to treat IMTs. Its invasiveness and aggressiveness and lack of universally recommended therapeutic protocol subjects IMT to a great paradoxical discussion. Yet, identification of distinct characteristics and collaborative work by multiple experts has opened pathways to produce outstanding results.

**References**


5. Surgical Pathology Criteria – Inflammatory Myofibroblastic Tumor. surgpathcriteria.stanford.edu : 2015