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Inflammatory myofibroblastic tumour, an unusual presentation in maxilla and paranasal sinuses: review of literature and a case report

Abstract

Inflammatory myofibroblastic tumours (IMT) are uncommon lesions, rarely affect the head and neck region. Its etio-pathogenesis and biological behaviour is still uncertain. IMT is just a reactive process or a true neoplasia is of great controversy. Because of its unpredictable biological behaviour and histopathological presentation clinically and radiologically it may simulate a malignant tumour. Though most of the IMT of head and neck shows a benign course but IMT of paranasal sinuses are highly aggressive in behavior with poor response to surgery, radiotherapy and chemotherapy, showing multiple recurrences and fatal outcome. Therefore management of IMT of maxillofacial region is challenging as there is no established protocol of treatment, but effort on individual IMT demonstrates its well response on combination regimen of prednisolone, methotrexate and celecoxib acid (cyclooxygenase 2 inhibitor) responds well and there is virtually total regression of the lesion. We hereby report a case of IMT in maxilla and paranasal sinuses and a review of its inflammatory versus neoplastic behavior.

Keywords: cyclooxygenase 2 inhibitor, inflammatory myofibroblastic tumour, maxillary swelling, methotrexate, prednisolone, prognosis, treatment

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Introduction

Inflammatory myofibroblastic tumour (IMT) is a rare pathology of unknown etiology. It was called inflammatory pseudotumor (IPT) until 1998, when the term inflammatory myofibroblastic tumour (IMT) was proposed as being a more descriptive name.[1] IMT and IPT terminologies are most confusing and interchangeably used due to very numerous similarities in histological presentations. But despite numerous similarities in histology/subtle differences such as marked spindle cell proliferation in IMT and prominent lymphoplasmacytic infiltration in IPT help to histologically differentiate them. Immunohistochemical markers are invaluable in differentiating both of them. Though there is no significant difference in the clinical standpoint and are considered synonymous.[2,3] Now it is belong to the group of soft tissue tumours and have been known by various synonyms; inflammatory pseudotumor, plasma cell granuloma, fibrous histiocytoma and sometimes low grade sarcoma or inflammatory fibrosarcoma.[4–15] It was referred to by several different terms until the World Health Organization (WHO) classified IMT as a distinct entity.[6] The diverse nomenclature is mostly descriptive and reflects the uncertainty regarding its true biologic nature of these lesions.[7] Therefore IMT is clinico-pathologically distinctive but biologically controversial entity, which was originally described as true neoplastic lesion.[5–8] Exact etio-pathogenesis is not known, though it is considered to be an exaggerated inflammatory reaction to tissue injury of unknown cause.[9] Recently the -concept of this lesion being reactive has been challenged based on the clinical demonstration of recurrences and metastasis and further cytogenetic evidence of acquired clonal chromosomal abnormalities.[10] Moreover the presence of human herpes virus-8 DNA sequences and the over expression of interleukin 6 and cyclin D1 have been reported in IMTs.[11] Then conception of inflammatory origin was refuted by some researchers. Later it was described may arise as an immunologic host reaction to stimuli such as microorganisms (e.g Epstein –Barr Virus, Human Herpes Virus-8), foreign bodies or neoplastic tissues, chronic inflammation and may even trauma.[12] Though in some studies found an association between trauma and IMT that may lead to reactive inflammation has been suggested but causation cannot be proven completely.[10–12] Therefore whatever the cause a localized derangement in the immune response after the initial insult may be an underlying mechanism.[13] IMT is characterized by solitary, well demarcated mass with fibroblastic or myofibroblastic spindle cell proliferation with varying degrees of inflammatory cell infiltration.[1–14] There are three basic histologic patterns are recognized:

a. Myxoid, vascular, and inflammatory areas resembling nodular fasciitis;

b. Compact spindle cells with intermingled inflammatory cells (lymphocytes, plasma cells, and eosinophils) resembling fibrous histiocytoma; and Dense plate-like collagen resembling a desmoid or scar.

These three patterns could overlap, or priority is given to (a) or (b), and this pathological classification method is universally accepted presently.[12] The differential diagnosis of the head and neck IMTs should include various benign and malignant spindle cell proliferations which may pose considerable histological overlap with IMTs. The main benign entities include nodular fasciitis, fibromatosis, myofibroma, myofibromatosis, solitary fibrous tumour, benign fibrous histiocytoma, Wegener's granulomatosis, neural and smooth muscle lesions; the malignant differential diagnostic entities include fibrosarcoma, myofibrosarcoma, low-grade myofibroblastic sarcoma, malignant fibrous histiocytoma, spindle cell carcinoma, sarcomatoid carcinoma, leiomyosarcoma, rhabdomyosarcoma, and malignant peripheral nerve sheath tumour (MPNST). If there was a predominant

lymphocytic and/or plasmacytic component, lymphoma and plasma cell neoplasms (plasmacytoma and multiple myeloma) also should be excluded. Therefore knowledge of the different histologic patterns of IMT with identification of a predominant inflammatory component and contributory immunohistochemical investigation may allow unquestionable and definitive diagnosis.[15] The majority of IMT lesions are present in the lungs. Extrapulmonary cases though rare e.g hepatobiliary tract, gastrointestinal tract, retroperitoneum, soft tissue of trunk, extremities, head-neck, including heart can be the primary site of origin.[10–14] In the head and neck, it accounts 14-18% of extra pulmonary IMTs and present different clinical manifestations according to their different locations.[12] The common sites it has been reported in orbit, epiglottis, endolarynx, tonsils, parapharyngeal spaces, maxillary sinus, submandibular region and oral cavity.[15,16] There is no age preference identified with equal incidence in male and female patients. In the oral cavity, IMTs have been reported in multiple locations like gingiva, tongue, hard palate, mandible, buccal mucosa and submandibular salivary gland. Clinically they are painless indurated mass, or swelling of relatively short duration or following a specific symptom related to the site of origin. Its aggressiveness mimics malignant neoplasms clinically, radiologically and histopathologically. They have no age preference, but the affected patients tend to be children and young adults.[10] These lesions most commonly recurr locally and rarely metastasize to distant sites.[14] Further IMT of maxillary sinus is very rare. It usually appears as a nonspecific mass that has been growing over a period of months or years. The most frequent symptom is a local swelling or pain usually associated with at least one sinus wall destruction.[15] Studies demonstrates IMT of head and neck specially maxillofacial region is exceptionally rare, with variable characteristics that ranges from frequently benign lesions to more aggressive variants and it is often mistaken as malignancy. The diagnosis is still difficult and based on the histological examination of the lesion.[17] Therefore to avoid any further confusion, World Health Organization (WHO) classified IMTs as tumours of intermediate biological potential due to a tendency of local recurrence and mild risk of distant metastasis.[15] Computed tomography (CT) scan and Magnetic resonance imaging (MRI) helps to define the extent of the lesion and invasive changes of the surrounding tissues contributing to the decision of treatment. Though IMTs in the head and neck region might be non- specific and often suggest infiltrative growth, aggressive malignant lesion or granulomatous disease.[10] Laboratory investigations may not reveal additional information; low Hb%, elevated erythrocyte sedimentation rate (ESR) are frequent findings.[12] Management of IMT is very challenging as there are no established treatment protocols for head and neck. IMTs of head and neck are generally considered benign lesions and usually cured by radical excision, steroids, irradiation and/or chemotherapy. CO_2 laser is new modality of treatment.[10] Though surgery is considered the first line for resectable lesions, postoperative large dose hormone therapy of the whole body should be administered for a long time incase of positive surgical margins and also routinely used in paediatric groups after surgery. Further it is reported some patients who are insentitive to hormone therapy (generally glucocorticoids) the chemo-radiation should be an alternate option.[12] Glucocorticoid, i.e. prednisolone is anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive in nature. It acts by downstream production of a number of proinflammatory cytokine and chemokine proteins, cell adhesion molecules and other key enzymes involved in the initiation and/or maintenance of the host inflammatory response.[18] Chemotherapy is also recommended when IMT is multifocal; invasive or shows local recurrence.[19] Though a combination of agents like cyclosporine, methotrexate, azathioprine and cyclophosphamide are commonly used with no significant role in IMTs.[11] These agents have also been used as an adjunct with non-steroidal anti inflammatory drugs (NSAID) and glucocorticoid. Combination therapy has shown good response in instances where single therapy had failed.[20] We hereby report a case of IMT in maxilla and paranasal sinuses and a review of its inflammatory versus neoplastic behavior.

Case report

A 26 year old female from Norshindhi, Dhaka, Bangladesh was admitted in the department of Oral and Maxillofacial Surgery on 22.12.14 at Dhaka Dental College Hospital, Mirpur- 14, Dhaka-1206, with a history of pain, occasional nasal bleeding and sensitivity on upper left lateral incisor; with a distinctive non tender bony swelling near to inner canthus. The lesion was 3x1.5cm_2 in size. The overlying skin colour was slightly blackish with a scar mark of stitches of previous surgical intervention (excisional biopsy). She had a past history of trauma 10-12 years back, at that time it was swollen and painful, which later subsided following conservative treatment. Then after seven years it reappears and again subsided without any specific treatment but third time at present it is persistent in nature and history of pain with occasional nasal bleeding with frontal heaviness. She had no sinonasal problem like nasal growth, obstruction etc., and no history of allergy. Her body weight is 57 kg and height is five feet and three inch. On palpation the swelling is firm in consistency, overlying skin is free but fixed to the underlying structures and tenderness is present. Local temperature is not raised. No paresthesia or anesthesia of this region. No regional lymph node palpable. Her general and systemic examination revealed nothing contributory. Routine blood investigation revealed accelerated erythrocyte sedimentation rate (ESR) i.e. average more than 100 mm of first hour and mild anemia. X-ray OPG revealed mild hazziness of left maxillary sinus. Cone beam computed tomography (CBCT) of head and face on dated 6.1.15 reveals extensive bone destruction i.e. perforation of outer cortex of maxilla, hard palate, lateral nasal wall, ethmoidal sinus etc. A provisional diagnosis of aggressive lesion of maxilla and paranasal sinus was considered. Though initial biopsy showed only hyperplastic squamous epithelium with inflamed fibrocollagenous tissue and inflammatory cell infiltrate without any evidence of malignancy. Further on radiological assessment by Cone beam computed tomography (CBCT), the lesion was found destructive in nature and had been growing rapidly. In the mean time the patient had developed severe pain, swelling of cheek, nasal fullness, bloody nasal discharge, frontal heaviness along with breathing problem. As no definitive pathological diagnosis could be established, the patient was considered for up front surgery. It was again explored after twenty two days along the previous scar mark. i.e. lateral rhinotomy incision and with fresh infraorbital extention, wide surgical excision was done, lining of maxillary sinus was removed . There was erosion of lateral wall of nose, perforation of floor of hard palate, lesion spreads up to ethmoidal sinus, here lesion was enucleated only. The specimen was sent for histopathological examination. On histopathological report shows proliferation of plum fibroblast cells and infiltrated with chronic inflammatory cells including occasional eosinophil. No evidence of malignancy was seen. The final diagnosis of inflammatory myofibroblastic tumour was confirmed by histopathological studies only as immunohistochemical (IHC) staining of the tissue section was not done due to financial constraint. Now after informed consent the

patient was blindly on a trial basis commenced on high dose (>20 mg/day) of oral prednisolone i.e. 30 mg/day was continued with gastric coverage for two months. This non-endocrine pharmacologic (therapeutic) dose was used to suppress inflammation. It also has anti-proliferative, vasoconstrictive and immunosuppressive effect; however there is no 'threshold' dose or treatment duration has been established due to less mineralocorticoid activity. e.g water retention property, which was undesirable; prednisolone was preferred. Before initiating long-term systemic steroid therapy a thorough history and physical examination was preferred to assess for risk factors or pre-existing conditions such as diabetes, cardiovascular diseases, gastro intestinal disorders, dyslipidaemia, affective disorders, osteoporosis etc. At a minimum, baseline measurement of body weight, height, and blood pressure (BP) were obtained along with laboratory investigations that include a complete blood count, blood glucose values, lipid profile and BMD (bone marrow density). The patient was advised to avoid exposure to serious infections, adopt lifestyle recommendations to minimize the risk of weight gain and eat a healthy balanced diet including adequate calcium intake and regular physical activity. The patient responded very well and resulted in symptomatic improvement. There was no evidence of recurrence both clinical and radiological assessment (i.e. by contrast CT scan). Then gradual tapering (2.5-5 mg decrements every 3-7 days until physiologic dose of 5mg/day) and followed by withdrawl of steroids done.[18] But after only one month later the patient had developed features of recurrences i.e. pain, blood stained nasal discharge, pain, frontal heaviness etc. despite the initial remission. Then a prompt diagnosis was made and treatment restarted with combination of drugs like both high dose prednisolone and once weekly low dose methotrexate (chemotherapeutic agent) and continued for six months. Then again slowly tapered prednisolone to a low maintenance dose and methotrexate remained the same. After dual agent combination therapy every six monthly contrast CT scan was repeated till date. The satisfactory response to single use steroid encourage us to attempted for combination drug and there after celecoxib acid (cyclooygenase 2 inhibitor-200mg/day)[21,22] was added for its anti inflammatory in action. Despite their beneficial effects we should keep in mind that the long–term systemic use of these agents has various hazards like osteoporosis, fracture, hyperlipidaemia, hypertention, hyperglycaemia etc. Clinical, radiological and inflammatory marker response was helpful in adjusting the dose and duration of treatment. There is virtually total regression of the lesion. The patient is currently on the same treatment and there is no recurrence since last two years and five months (Figures 1−6).

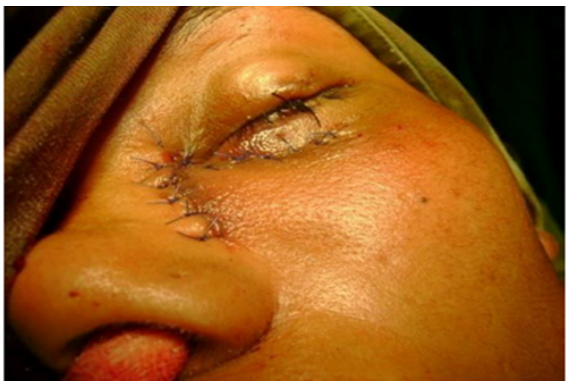

Figure 1 Showing site of lesion with stitches.

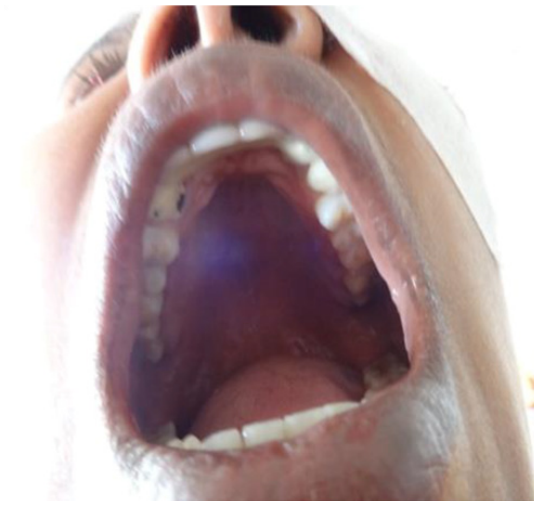

Figure 2 Intraoral picture of palate with no perforation or opening through mucoperiosteum.

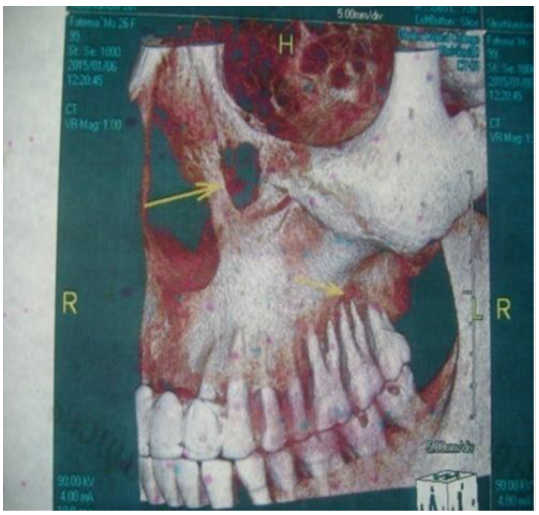

Figure 3 CBCT showing perforation of outer cortex of left maxilla.

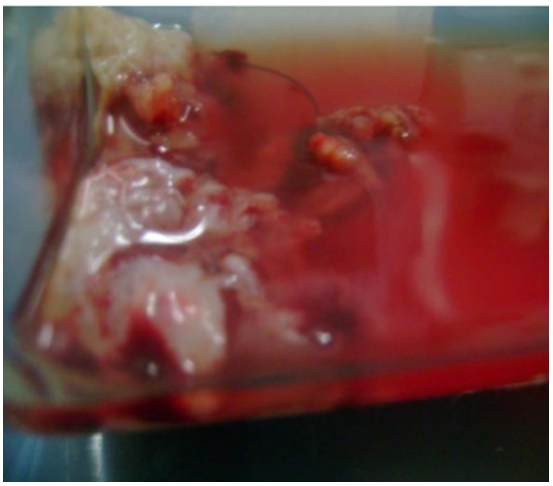

Figure 4 Post surgical specimen within a glass container.

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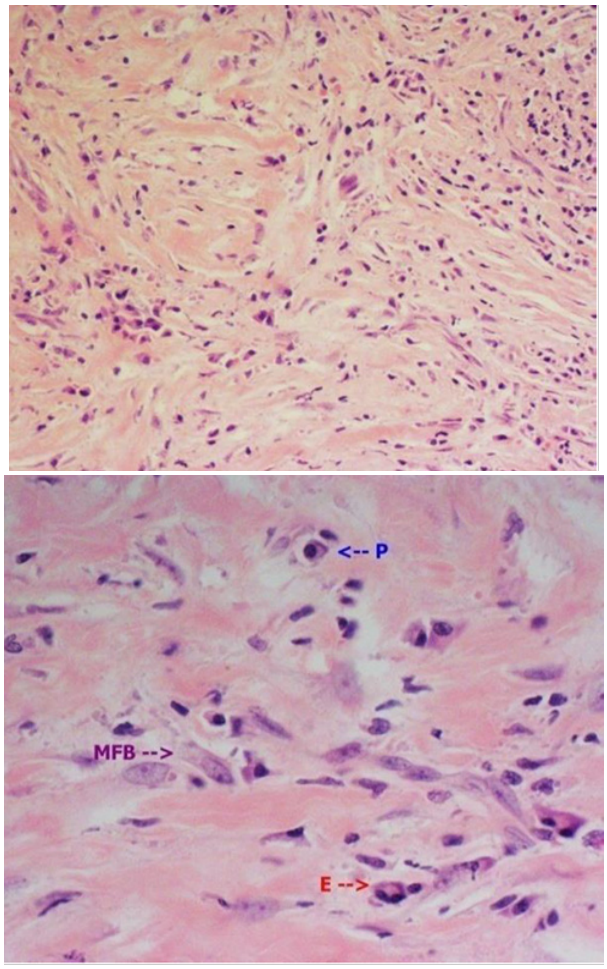

Figure 5&6 Showing proliferation of plump of fibroblast cells, infiltrated with chronic inflammatory cells and occasional eosinophil.

Discussion

The aggressive aspect of paranasal sinus inflammatory myofibroblastic tumours (IMT) is a diagnostic challenge. It is quite common for patients with IMT to undergo multiple biopsy.[10] Though it is considered to be a reactive myofibroblastic proliferation of unknown etiology.[22] It mimics malignant neoplasm clinically, radiologically and histopathologically.[10] Similarly when the patient at the late stage of disease progression i.e. just before last surgery had developed pain, nasal bleeding, heaviness etc. and it was very confusing indeed, whether it may be a malignant case or not. However the confirmed diagnosis of IMT could not be based on clinical findings only, supplemental diagnostic tool like histological studies were required.[15] Again it was reported IMT lesions may show neoplastic features such as persistent local growth, recurrence, and metastasis, hence few authors consider it as a low-grade inflammatory fibrosarcoma.[10] Further it is difficult to diagnose solely on histopathology because of its complicated pathological characteristics[15]and the patient had no immunohistochemistry studies. Fibrosarcoma was excluded due to lack of malignant features, collgenous areas and herring bone pattern that characterize it. Additionally it typically lacked a significant inflammatory infiltrate.[23] Palashar S et al.[10] also declares the concept of this lesion (IMT) being reactive has been challenged based on the clinical demonstration of recurrences and metastasis and cytogenetic evidence.[10] Though most of the IMT of head and neck shows a benign course but IMT of paranasal sinuses are highly aggressive in behavior with poor response to surgery, radiotherapy and chemotherapy, showing multiple recurrences and fatal outcome.[24,25] Thus early primary radical resection is always preferred, if the anatomical location and surrounding structures involved are permissible. Radiation therapy has been reported for unresectable and recurrent cases and as there is no standardized chemotherapeutic regimens till now. So the benefit of chemotherapy and radiation therapy may yet be unproven, but high-dose steroid therapy was effective in some cases.[15] Here the patient showed mixed benign and malignant feature of the neoplasm and the observed remission to initial steroid therapy and relapse of on withdrawal was keeping in line with poorly understood characteristics of the lesion. Again IMTs originating from extrapulmonary sites is known to show a more aggressive behavior and the aetiology of this site related aggressiveness is not well understood. Therefore the correct recognition of the lesion is important and recognizes the distinction among them in order to provide better guidelines for treatment and outcome. Though trial evidence for medical treatment like steroid and methotrexate used for IMT is lacking routine recommendation in inoperable cases and our experience suggest that it is reasonable alternative with possible favourable outcome. Medical treatment has been guided by clinical and radiological response. Our experience demonstrates that steroids with methotrexate and celecoxib acid in combination may be effective regimen for surgically unresectable inflammatory myofibroblastic tumour of maxilla and paranasal sinuses. Again duration and intensity of treatment should be individualized guided by clinical, biochemical and radiological response.

Conclusion

Inflammatory myofibroblastic tumour (IMT) is just a reactive process or a true neoplasia is of great controversy. Because of its unpredictable biological behavior and histopathological presentation. Clinically and radiologically it may simulate a malignant tumour. But studies on IMT demonstrates its distinct clinico-pathological entity, which responds well on combination regimen of prednisolone, methotrexate and celecoxib acid (cyclooxygenase 2 inhibitor). So early diagnosis and careful follow up of these cases are mandatory.

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Conflicts of interest

Author declares that there is no conflict of interest

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