Inflammatory myofibroblastic tumor of paranasal sinuses

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ABSTRACT

Inflammatory myofibroblastic tumors (IMTs) are clinico-pathologically distinctive but biologically controversial entities; they rarely affect the head and neck region and usually follow a benign clinical course after radical excision. We reviewed the literatures of IMTs and present a rare case of IMT arising from the maxillary paranasal sinus of an 11-year-old girl. Moreover, we elaborate on the morpho-immunophenotypic characteristics of this lesion. Microscopic examination revealed a spindle cell proliferation set in a highly vascular stroma with numerous inflammatory cells. Tumor cells were immunoreactive for vimentin, and smooth muscle actin, negative for desmin, S-100, p53, Cyclin D1, and bcl-2. The potential neoplastic nature of this lesion was substantiated by the strong diffuse immuno-expression of ALK-1 protein, a marker that has been linked to neoplastic transformation. The lesion was excised completely by a CO_2 LASER as a new treatment modality and the patient manifested no evidence of disease recurrence at 10-months recall.

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Inflammatory myofibroblastic tumors (IMTs) were first observed in the lung and described by Bunn in 1939. It was named as inflammatory pseudotumor by Umiker et al in 1954 because of it mimics to malignant neoplasm clinically, radiologically and histologically. Inflammatory myofibroblastic tumors are clinicopathological distinctive but biologically controversial entities. Various pathogenetic backgrounds have been proposed as initiating factors such as reactive, infectious, autoimmune and neoplastic processes, but the etiology of most remains unknown. Inflammatory myofibroblastic tumors rarely affect the head and neck region. To date, 19 cases of IMT have been described in the head and neck, 9 have been described in the oral cavity with the mandible being the site of predilection, and a few well documented IMTs have been found in the larynx.[1-4] In general, they follow a benign clinical course, with favorable outcome after radical local excision; however, invasive, locally recurrent, and metastatic forms of abdominal, mediastinal, and paranasal sinuses IMTs have also been reported.[1] The authors reviewed the literature about this interesting lesion and wished to describe their successful use, for the first time 'to the best of their knowledge' of the CO_2 laser in resecting such rare paranasal sinus tumor and also to report absence of tumour recurrence, despite its strong expression of ALK-1 protein.

Case Report. An 11-year-old Bahraini girl, not known before to have any medical illness or being on any medical therapy, presented to the ENT clinic on July 2005, complaining of a left sided nasal blockage, pain over the nasal region and epistaxis of 2 weeks' duration. Examination of the nose revealed an unfamiliar appearance of an inflamed, nasal polyp. The polyp was found friable when a small biopsy from the tip of this polyp was taken under local anesthesia for histologic examination at time of consultation in the clinic. Computed topography (CT) scan showed a soft tissue mass in the left maxillary sinus extending to and filling the ipsilateral nasal cavity (**Figure 1**). A topical steroidal nasal spray was prescribed to use until the next visit after one week after. The histology report revealed as a non-diagnostic infarcted tissue piece. Three weeks later, as scheduled, she reported back to the clinic with a worsening of pain intensity as well as increasing in the size of the polyp. She was admitted to the hospital and a radical excision of the lesion was performed by a CO_2 laser under general anesthesia. The intra-operative findings revealed a 3.5 x 2.0 x 1.0 cm, highly vascular, friable lesion occupying

the whole anterior two-third of the left nasal cavity, and appeared emerging from the lateral wall of the inferior meatus. The cartilaginous part of the septum was found to be pushed and appeared deviated to the right side. The lateral wall of the left nasal cavity was intact. The whole mass was excised and its root along with the adjacent mucosa was ablated by CO_2 laser. The left maxillary sinus was examined again endoscopically via a Caldwell-Luc incision and found to be clear. The postoperative course was uneventful and the patient was discharged on the second day. She was kept on a normal saline nasal douches, local vasoconstrictor and antibiotics for one week. On subsequent fortnightly postoperative follow-up visits, her nasal cavity was found to be clear. Two months later, a repeat CT scan revealed residual, moderately hypertrophied soft tissue density occupying the left maxillary antrum (**Figure 2**). Subsequently, this tissue area was biopsied at different points via Caldwell-Luc approach and through left maxillary osteotomy in order to rule out tumor recurrence. Histological examination proved this biopsy as a minimally inflamed mucosal tissue only. Despite the inconclusive histology of the very initial small biopsy that has been taken in the clinic, the polypoidal nasal mass that was excised later was found very impressive; it was partly ulcerated, composed of proliferating spindle cells and showed only occasional mitoses. The lesion had 2 main growth patterns. A predominant granulation tissue/nodular fasciitis-like component formed by loose pale eosinophilic stellate and plump spindle cells having elongated, slightly pleomorphic nuclei with one or more small nucleoli (**Figure 3**). These spindle cells were arranged haphazardly within a myxoid or oedematous background. The stroma was markedly vascular and densely infiltrated by unevenly distributed inflammatory cells such as lymphocytes, plasmacytes and occasional neutrophils. Areas of extravasated red blood cells were also present. The less represented spindle cell growth pattern was characterized by a compact structure-less cellular proliferation with scant intervening stroma. Neither ganglion-like cells nor apparent collagen deposition was seen. Calcification, stromal epithelial and glandular structures were all absent. Focal areas of ischemic infarction were noted at the distal parts of the polypoidal lesion. Special chemical stains for mycobacteria, nocardia, and common fungal infection were all negative. The tumor spindle cells showed strong diffuse immunohistochemical (IHC) reaction to vimentin, and smooth muscle actin and focal strong reaction to CD 68. In addition, a strong diffuse IHC expression of ALK-1 specific IMTs mutation was also present. Desmin, EMA, MNF-116, S-100 protein, p53, Cyclin D1 and bcl-2 were all negative.

Ki-67 stained 10-15% of spindle cell nuclei. MDM2, CDK4, pRb, EBV-LMP, and HHV-8 were

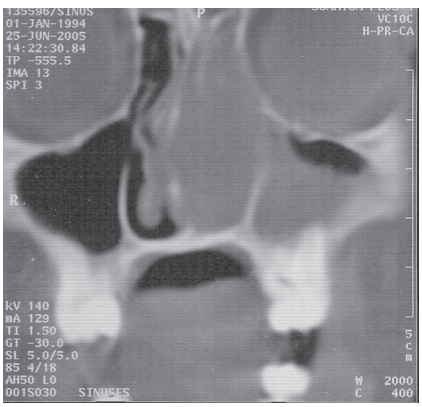

Figure 1 - Computed topography scan showing a soft tissue mass in the left maxillary sinus extending to and filling the ipsilateral nasal cavity.

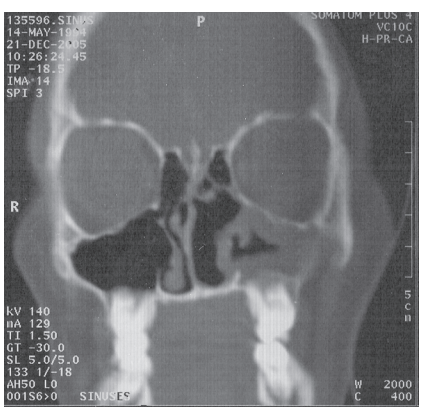

Figure 2 - Repeated CT scan after 2 months of the operation showing only minor mucosal soft tissue swelling at the maxillary antrum.

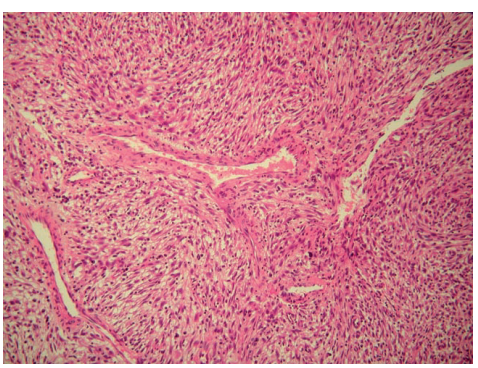

Figure 3 - Photomicrograph showing part of the nasal polyp with a predominant granulation tissue-like component formed by loose pale eosinophilic stellate and plump spindle cells having elongated, slightly pleomorphic nuclei with one or more small nucleoli (hematoxylin and eosin stain x20).

not performed. The background inflammatory cell component was mixed and polyclonal, included mainly kappa light chain producing B-lymphocytes and plasma cells, numerous reactive CD3 positive T-lymphocytes, few neutrophils and occasional eosinophils.

Discussion. Inflammatory myofibroblastic tumors (IMTs) are clinico-pathologically distinctive but biologically controversial entities. Initially they were described in the lungs but later on, reported to occur in nearly every site in the body, including the liver, spleen, lymph nodes, gastrointestinal tract, CNS, and genito-urinary system. These lesions have been widely known as inflammatory pseudotumors, but other synonyms were also in use, for instance, pseudosarcomatous fibromyxoid tumors, atypical myofibroblastic tumors, atypical fibromyxoid tumors, pseudosarcomatous myofibroblastic proliferation, plasma cell granulomas or plasma cell pseudotumors, nodular fasciitis, inflammatory follicular dendritic cell tumors of the spleen and liver, myofibroblastic neoplasia, myofibroblastoma, xanthomatous pseudotumors, and inflammatory myofibroblastic tumors. The latter includes inflammatory fibrosarcoma.[2,8] Such lesions rarely affect the head and neck region and when they do, they commonly involve the oral cavity, orbit, nasal cavity, maxillary sinuses, infratemporal fossa; parapharyngeal space and pterygopalatine fossa of nasopharynx, major salivary glands, clivus, larynx and trachea.[2,9] Clinically, IMTs are usually benign lesions, most commonly present as an incidentally discovered painless, indurated mass or swelling of relative short duration, or following specific symptoms related to the site of origin. They have no age preference, but affected patients tend to be children or young adults.[4] In the nasal cavity and paranasal sinuses, the initial presenting symptom is usually a non-specific sinonasal mass, which tends to grow over a period of months or years. The clinical or endoscopic findings may demonstrate a swelling covered by normal mucosa, an edematous mucosa, hypertrophic concha, hemorrhagic rhinorrhea, grey-tan exophytic, nodular or polypoidal lesion that may extend deeply in to the adjacent structures from which it arises. The size ranges from 1.5 to 9.0 cm; the consistency is also variable, either soft or firm depends on the stromal tissue and the associated hemorrhage. Cavity obstruction with or without wall destruction is usually seen in paranasal sinuses lesions. Unlike their counterparts at other locations, their presentations generally do not include non-specific systemic symptoms, such as unexplained fever, weight loss, malaise or associated laboratory abnormalities of hypochromic normocytic anemia, polyclonal hypergammaglobulinemia, thrombocytosis, plasmacytosis, or increased interleukin-6, interleukin 1-B and cyclin D1 production. The last 3 cellular products are the apparent mediators of the clinical and laboratory abnormalities which may persist for months before the diagnosis and improve after resection.[3,10] Computerized tomography scan and/or magnetic resonance imaging of IMTs in the head and neck region might be non-specific, and often suggest either infiltrative growth with aggressive malignant potential or granulomatous disease.[4,5] Sinusoidal IMTs when they show aggressive appearances, tend to be associated with bony changes such as erosion, remodeling and sclerosis. Magnetic resonance images are usually isointense compared to muscle on T1-weighted images and relatively hypointense T2 signal compared to most other tumors. Variable contrast enhancement is also reported. Computerized tomography scan has proven valuable in defining the extension of IMT, their response to treatment and perhaps suggesting the pathogenesis too. Therefore, correct diagnosis is vital to prevent unnecessary over treatment.[1,6] Histologically, IMT is characterized by bipolar or stellate shape myofibroblastic spindle cell proliferation, admixed with a prominent polyclonal infiltrate of lymphocytes, plasma cells, and neutrophils, in a loose myxoid or oedematous stroma. Three basic histological patterns, none of which appears to have a distinct association with the clinical behavior, have been described; namely: 1) inflammatory granulation tissue-like myxoid/ vascular pattern 2) nodular fasciitis-like compact spindle cell pattern with a haphazard fascicular and/or storiform areas and variation of cellular density; and 3) a fibrous scar-like hypocellular pattern, of densely collagenized stroma. The 3 patterns may well be represented within the tumor, often blending into one another, with one or 2 patterns predominating. The spindle cells lack the cytologic atypia and nuclear hyperchromasia of sarcomas.[4,5,7] Immunohistochemistry is usually utilized to confirm the myofibroblastic phenotype of the tumor spindle cells, which are typically reactive to vimentin (99%) and smooth muscle actin (92%). Other myogenic markers positivity is less consistent including muscle specific actin (89%) and desmin (69%). In addition, the spindle cells may be focally positive to epithelial markers such as cytokeratin and EMA (36%). CD68 can be also focally positive (25%). Inflammatory myofibroblastic tumors are typically negative to myoglobin and S-100 protein. Only few reported splenic and liver IMTs, particularly those in immunosuppressed patients were found to be positive to EBV-LMP and HHV-8.[8] In our case, the tumor spindle cells showed strong diffuse vimentin and smooth muscle actin positivity consistent with a

myofibroblast immunophenotype. Desmin, another myogenic marker was negative as expected. A strong focal positive reaction to CD 68 was also noted; epithelial markers EMA and MNF-116 pan-cytokeratin were negative. Nerve cell differentiation marker, S-100 protein was also negative. In addition, the potential neoplastic nature of this lesion was substantiated by the strong diffuse immunohistochemical expression of ALK-1 specific IMTs mutation, a marker that has been linked to neoplastic transformation, this holds true despite negative reaction to tumor suppressor gene (p53), cell cycle regulatory protein (Cyclin D1) and anti-apoptosis gene (bcl-2). Noteworthy, the tumor spindle cells showed only low (10-15%) Ki-67 nuclear staining. MDM2, CDK4, pRb are other markers used to assess for the neoplastic potential of this lesion, but were not available to us. We did not perform any stains for Epstein-Barr virus (EBV-LMP), and HHV-8, because their positive reaction observation is unusual in our case and because it has been only rarely noted in few subsets of non-head and neck IMTs such as those arising in lymph nodes, spleen and liver of immunosuppressed children and young adults.[3] The background cellular infiltrate was confirmed to be of a mixed polyclonal inflammatory nature that includes mainly kappa light chain producing B-lymphocytes and plasma cells, numerous reactive CD3 positive T lymphocytes, few neutrophils and occasional eosinophils. Treatment and clinical outcome are generally favorable. Acute lesions typically respond to high dose of corticosteroids but chronic lesions, which tend to have more fibrosis, generally do not respond to medical therapy. No relationship has been found between the duration of signs and symptoms and the degree of fibrosis.[12] Radical excision is curative in more than 90% of extrapulmonary IMTs, including head and neck lesions. The frequency of local recurrence is approximately 25%. In the head and neck region, only one case of IMT of the maxillary sinus showed extension to pterygopalatine fossa following corticosteroid treatment alone without surgical intervention. Very large lesions, or those arising in areas difficult to excise completely, such as mesenteric, omental, peritoneal, pelvic, or retroperitoneal sites, and paranasal sinuses, tend to recur, with a potential for metastatic spread in rare instances. Pulmonary and brain metastasis were reported.[5,9,13,14] For non sinusoidal IMT, response to steroids and antibiotics is often unpredictable. Radiation therapy has been tried in unresectable cases. Many believe that chemotherapy in the form of cyclosporine, methotrexate, azathioprine and cyclophosphamide has little role.[15] For sinusoidal IMT, surgery followed by corticosteroids in cases of incomplete excision is the treatment of choice. Radiotherapy is reserved only for patients whom surgery and steroids are unsuccessful or contraindicated.[2] Etiology and pathogenesis of IMT remain incompletely understood. It is alleged that these tumors partly represent an exuberant reparative reaction to previous trauma or chronic irritation; yet other subsets of IMTs have been found to be associated with autoimmune mechanisms such as vasculitis. Many authors found that IMTs are most probably linked with infection initiating mechanisms. The list of infectious agent is expanding, such as *Mycobacteria, Actinomycetes, Nocardia, Mycoplasma, E. coli, Klebsiella, Bacillus sphaericus, Pseudomonas,* HIV, *Helicobacter pylori,* Epstein-Barr virus, and human herpesvirus 8, all have been reported.[7,8] Cytogenetic and molecular studies point to the possibility that some subsets of IMTs are in fact true monoclonal neoplasms; not only that, but invasive, locally recurrent, and metastatic forms of abdominal, mediastinal, and paranasal sinuses IMTs have also been reported.[1] In contrast to the latter, there are others who believe that the reported cases of metastatic IMTs represent cases of multicentric disease and not a true metastasis.[4] The neoplastic clinical behavior is reflected by some cytogenetic and immunofluorescence aberrations especially chromosome 2p23 involving the anaplastic lymphoma tyrosine kinase (ALK) receptor and its fusion with clathrin heavy chain. This abnormality has been detected in up to 50% of soft tissue IMTs. Other abnormalities such as t(2,17) (p23,q23), tropomyosin 4 (TPM4), tropomyosin 3 (TPM 3), t(p25;p23), cysteinyl-tRNA synthetase and Ran-binging protein 2 have also been identified in IMT.[9,11] Differential diagnosis of IMTs in the head and neck mainly includes lesions composed of myofibroblast and fibroblasts, which may pose considerable morphological overlap with IMTs. The clinicopathologic settings such as the patient's age and gender, number and location of the tumor needs to be considered as IMTs are uncommon and a variety of lesions of diverse nature and etiologies can share one or more of the 3 characteristic spindle cell morphologic growth patterns of IMTs and have been indeed referred to as IMF tumor. The main benign entities include nodular fasciitis, Wegner's granulomatosis and sarcoidosis, inflammatory fibroid tumor, meningioma, xanthogranulomatous inflammation, fibromatosis and Riedel's thyroiditis; the malignant differential diagnostic entities include cytokeratin negative spindle cell squamous carcinoma, leiomyosarcoma, Hodgkin's lymphoma, inflammatory fibrosarcoma, inflammatory malignant fibrous histiocytoma, and angiosarcoma.[1,4,13]

In summary, IMTs of the head and neck region are generally benign lesions and usually cured by radical

excision. Steroids, irradiation and/or chemotherapy can be used if the lesion can not be completely excised. CO_2 LASER is a new modality of treatment that was used in this case. There are cases that clinically and radiologically, may simulate malignant tumors, but the bland histologic appearance of proliferating spindle cells and plasma cells rich inflammatory background is characteristic. Cellularity, mitotic counts, and extent of inflammation do not appear to be prognostic markers; in contrast, some authors state that at least a subset of IMTs represents true neoplasia and found that cytologic atypia, presence of ganglion-like cells, p53 expression and DNA aneuploidy may be useful for identifying tumours that are more likely to pursue an aggressive clinical behavior with recurrence or malignant transformation.[10] It appears that an 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, morphologic, immunohistochemical or prognostic difference is found associated with the ALK status of the IMT. Other myofibroblastic proliferative cases such as nodular fasciitis and desmoid fibromatosis do not express ALK-1.[11]

References

1. Gale N, Zidar N, Podboj J, Volavsek M, Luzar B. Inflammatory myofibroblastic tumour of paranasal sinuses with fatal outcome: reactive lesion or tumour. ***J Clin Pathol*** 2003; 56: 715-717.
2. Ruaux C, Noret P, Godey B. Inflammatory pseudotumor of the nasal cavity and sinuses. ***J Laryngol Otol*** 2001; 115: 563-566.
3. Chan JKC. Inflammatory pseudotumor: a family of lesions of diverse nature and etiologies. ***Adv Anat Pathol*** 1996; 3: 156-159.
4. Mills SE, Gaffery MJ, Frierson HF. Tumors of the Upper Aerodigestive Tract and Ear. In: Rosai J, Sobin LH, editors. Atlas of Tumor Pathology textbook. 3rd series. Washington: Armed Force Institute of Pathology; 2000. p. 280-282.
5. Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. ***Am J Surg Pathol*** 1995; 19: 859-872.
6. De Vuysere S, Hermans R, Sciot R, Crevits I, Marchal G. Extraorbital inflammatory pseudotumor of head and neck: CT and MRI findings in three pateints. ***Am J Neuroradiol*** 1999; 20: 1133-1139.
7. Brook S, John K, Nikolaos G. Oral inflammatory myofibroblastic tumour demonstrating ALK, P53, MDM2, CDK4, pRb, and Ki-67 immunoreactivity in an elderly patient. ***Oral Surgery*** 2005; 99: 716-726.
8. Gomez-Roman JJ, Ocejo-Vinyals G, Sanchez-Velasco P, Nieto EH, Leyva-Cobian F, Val-Bernal JF. Presence of human herpesvirus-8 DNA sequences and overexpression of human IL-6 and cyclin D1 in inflammatory myofibroblastic tumor (inflammatory pseudotumor). ***Lab Invest*** 2000; 80: 1121-1126.
9. Lawrence B, Perez-Atayde A, Hibbard MK, Rubin BP, Dal Cin P, Pinkus JL, et al. TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. ***Am J Pathol*** 2000; 157: 377-384.
10. Hussong JW, Brown M, Perkins SL, Dehner LP, Coffin CM. Comparison of DNA ploidy, histologic, and immunohistochemical findings with clinical outcome in inflammatory myofibroblastic tumors. ***Mod Pathol*** 1999; 12: 279-286.
11. Cook JR, Dehner LP, Collins MH, Ma Z, Morris SW, Coffin CM, et al. Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor: a comparative immunohistochemical study. ***Am Surg Pathol*** 2001; 24: 1364-1371.
12. Sclanfani AP, Kimmelman CP, McCornick SA. Inflammatory pseudotumor of the larynx: Compression with orbital inflammatory pseudotumor, with clinical implication. ***Otolaryngol*** 1993; 109: 548-551.
13. Lopez I, Grande J, et al. Inflammatory myofibroblastic tumour of the larynx. ***J Laryngol Otol*** 2001; 115: 856-858.
14. Dehner LP. The enigmatic inflammatory pseudotumors: the current state of our understanding, or misunderstanding. ***J Pathol*** 2000; 192: 277-279.
15. Narla LD, Newman B, Spottswood SS, Narla S, Kolli R. Inflammatory pseudotumor. ***Radiographics*** 2003; 23: 719-729.