Oral Health Case Reports

Naryana, et al., Oral health case Rep 2016, 2:2
DOI: 10.4172/2471-8726.1000118

Case Report Open Access

Oral Inflammatory Myofibroblastic Tumor: Two Additional Cases and Literature Review

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Rec date: May 09, 2016; **Acc date:** June 01, 2016; **Pub date:** June 06, 2016

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Abstract

OIMT poses a diagnostic challenge as it is part of the vast spectrum of spindle cell neoplasms. It is a controversial tumor composed of a proliferation of myofibroblasts intermingled with an inflammatory cell infiltrate composed of lymphocytes, plasma cells, and eosinophils in focal areas of collagenous stroma. Before this nomenclature was proposed by World Health Organization (WHO) in 1994, this entity was defined by a variety of names such as: inflammatory pseudotumor, histiocytoma, plasma cell histiocytoma complex, plasma cell granuloma, fibrohistiocytoma, xanthomatous granuloma, myxoid hamartoma, xanthomatous pseudotumor, spindle cell pseudotumor, inflammatory fibrosarcoma, benign myofibroblastoma, and inflammatory myofibroblastic proliferation. WHO has classified OIMT as an intermediate soft-tissue myofibroblastic neoplasm according to its well reproducible histological morphology. The first case was reported in the lungs and though it may be found anywhere in the body, the lung, liver and gastrointestinal tract are the most common sites of involvement. In the head and neck region, it has been reported in the orbit, larynx, parapharyngeal spaces, maxillary sinus, submandibular region and the oral cavity. Oral lesions may be intraosseous or in the soft tissue. The etiology is controversial.

Keywords: Oral inflammatory Myofibroblastic tumor, Spindle cell tumor, Anaplastic Lymphoma Kinase (ALK).

Introduction

Benign and malignant spindle cell neoplasms of the oral cavity may be of epithelial, mesenchymal or odontogenic origin. These can occur peripherally in the soft tissue or centrally in the jaw bones. Due to their vast range of origin, these tumour's frequently impose a diagnostic challenge. As the name suggests, inflammatory myofibroblastic tumor (OIMT) is a spindle cell tumor of myofibroblastic proliferation with varying amounts of inflammatory infiltrate. It is a relatively rare tumor. To date, only thirty two cases in the oral cavity have been reported in the English literature. A majority of oral cases are benign. Definitive diagnosis is reached by thorough histopathologic and immunohistochemical examinations. Treatment of choice is surgery [1]. Long term follow-up is mandatory due an unpredictable behaviour. We present two cases of oral inflammatory myofibroblastic tumor. The first case presented as a maxillary intraosseous radiolucency in a 13 year old girl and showed anaplastic lymphoma kinase (ALK; 2p23) gene rearrangement. The second case presented as a peripheral lesion on the retromolar area in a 27 year old male and did not show ALK (2p23) gene rearrangement. This paper, in addition to the literature review also discusses the usefulness of ALK positivity in diagnosis as well as treatment of OIMT [2].

Case Reports

We are reporting two cases from UNMC, College of Dentistry, oral pathology laboratory archival material. Case 1 was diagnosed in 2008 with fluorescence in situ hybridization study. Case 2 was diagnosed in 1997 following opinions from three different pathologists. One pathologist thought the lesion represented an OIMT while the other favored a reactive lesion, specifically a myofibroblastic proliferation. Finally, the third pathologist felt the lesion was consistent with an inflammatory pseudotumor. Fluorescence in situ hybridization study was done in 2015 for assessing the reactivity of ALK in this case.

Case 1

A 13 year old girl presented with a 1.0 cm radiolucency of unknown duration in the furcation area of #3. The radiolucency was ill defined and the roots of teeth #3 and #2 were resorbed, with areas of erosion extending into the maxillary sinus (Figure 1). The clinical differential diagnosis included aggressive lesions, ameloblastoma, central giant cell granuloma and malignancy. The tissue submitted for biopsy included tooth #3 and multiple tan soft tissues measuring 2 1.3 0.3 cm in aggregate. Microscopic examination showed bland spindle cells arranged in a story form pattern in a collagenous stroma. The spindle cells showed vesicular nuclei and mild nuclear atypia and occasional mitotic figures (Figures 1-7) [3].

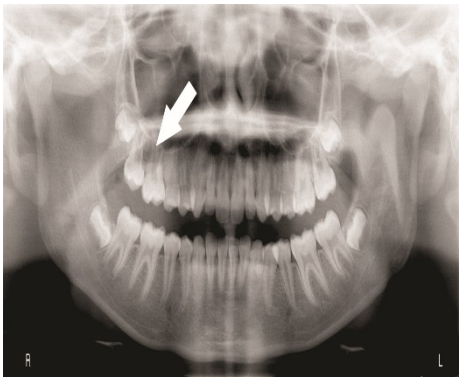

Figure 1: Pantomograph showing ill-defined radiolucency exhibiting resorption of roots of #3 (arrow) and extending upto the floor of the maxillary sinus (Case 1).

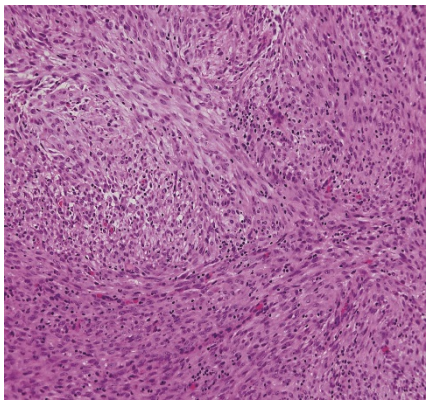

Figure 2: Histology showing spindle cells arranged in a storiform pattern with sprinkling of inflammatory cells. ((Case 1: hematoxilin-eosin stain x 10x).

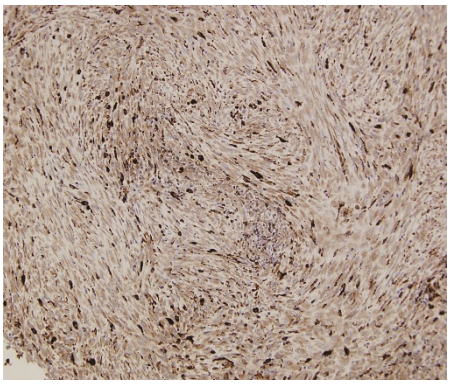

Figure 3: Histology showing CD 68 positive Spindle cell (Case 1: Immunohistochemistry x 20x).

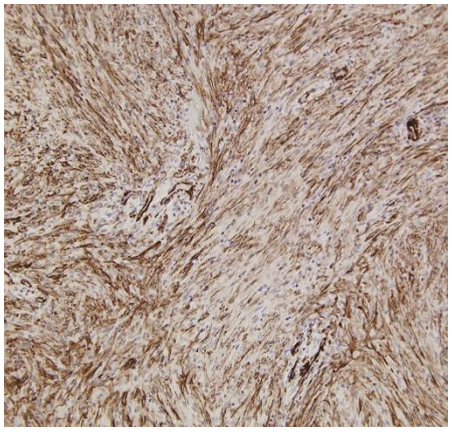

Figure 4: Histology showing SMA positive Spindle cell (Case 1: Immunohistochemistry x 20x).

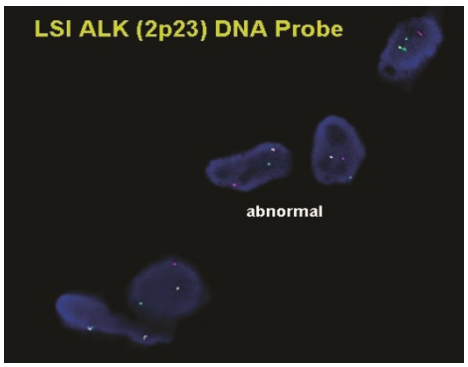

Figure 5: Note the split of one set of red and green signals indicating a rearrangement of the ALK gene locus (Case 1: LSI ALK (2p23) DNA probe).

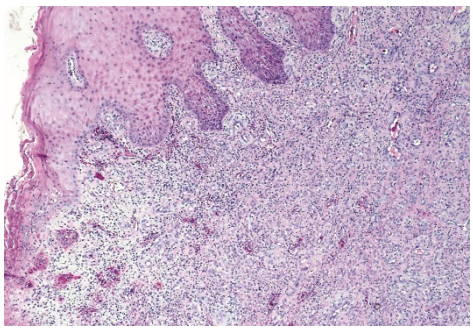

Figure 6: Histology showing ulcerated surface mucosa and fibrous connective tissue with spindle cells and inflammatory cells. ((Case 2: hematoxilin-eosin stain x 10x).

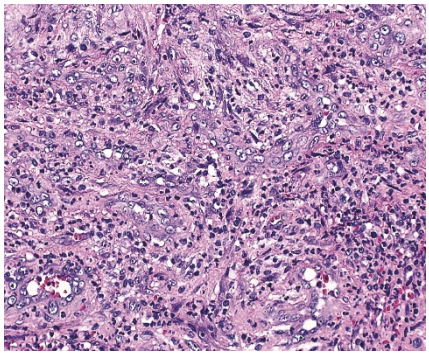

Figure 7: Histology showing fibrous connective tissue with spindle cells and inflammatory cells. (Case 2: hematoxilin-eosin stain x20x).

The stroma showed moderate inflammatory infiltrate consisting of lymphocytes and plasma cells. Cholesterol clefts, foreign body giant cells and foamy histocyte's were also seen in the fibrous stroma. The spindle cells were positive for CD68 and smooth muscle actin and negative for S100, pan cytokeratin and CD34. To confirm the diagnosis of OIMT fluorescence in situ hybridization study was done. It demonstrated 73% ALK (2p23) rearrangement confirming the diagnosis of OIMT. The surgeon was informed that as this tumor showed a recurrence rate of 23-37%, it should be treated aggressively. The patient was thereafter referred to an Ear nose and throat surgeon and was lost to follow-up (Table 1).

Author	Age (years)	Sex	Site	Size (cm)	Duration	Follow-up	ALK-1
Liston et al. [19]	4	F	Buccal mucosa	4 5	2 weeks	6 m; NED	-
	2	F	Buccal mucosa	3 5	4 days	10 m; NED	
	6	M	Buccal mucosa	4 5	1 day	NA	
Earl et al. [20]	44	M	Buccal mucosa	NA		2 yrs; NED	-
Ramachandra et al. [21]	77	F	Buccal mucosa	1.5	5 months	28 yrs; NED	-
Shek et al. [17]	20	M	Right cheek	2.0 diam.	1 month	13 m; NED	-
	36	F	Left maxilla	NA	1 year	13 m; NED	
Ide et al. [22]	68	F	Buccal mucosa	0.5 0.6	Few years	NA	-
Ide et al. [23]	43	F	Retromolar area	1.0 2.3	1 m	1 yr; NED	-
Cable et al. [24]	29	F	Hard palate	1.8 1.8	8 wks.	NA	-
Ide et al. [25]	27	M	Tongue	1.7	4 m	NA	-
Pankaj et al. [26]	-	-	Tongue	-	-	NA	-
Jordan et al. [27]	23	M	Mandible	1.0	1 m	NA	-
Fang et al. [28]	23	M	Retromolar area and masseter muscle	2.5 4.5	1 m	6 m; NED	
Brooks et al. [2]	82	F	Mandible	5.0 5.0	2 m	18 m; NED	+ ve
Poh et al. [5]	42	F	Mandible	3.0 diam.	-	6 M; NED	+ ve
Johann et al. [30]	33	M	Mandible	3 2 2	-	28 m; NED	
Oh et al. [12]	20	F	Mandible	-	3-4 m	22 M; NED	
Xavier et al. [31]	23	F	Floor of mouth	3.0 diam.	3 wks.	2 yrs; NED	- ve
Eley et al. [13]	29	M	Maxilla	5.0 diam.	1 m	6 yrs; NED	???
Satomi et al. [32]	14	F	Gingiva	3 2	3 m	10 yrs; NED	- ve
Binmadi et al. [33]	40	F	Gingiva	1.5 1.2	-	4 m; NED	+ ve
Palaskar et al. [4]	19	M	Right side of face	-	3 m	6 m; NED	+ ve
Tefera [11]	16	F	Right mandible	10	3 yrs.	1 yr; NED	-

Lourenco et al. [1]	14	M	Tongue	2 diam.	1 m	5 yrs; NED	-
Ekici et al. [34]	75	M	Tongue	4	4 m	1 yr; NED	-
Rautava et al. [15]	11	F	Maxilla	-	3m	3 yrs; NED	+ ve
Stringer et al. [10]	16	M	Mandible	-	3.5 m	6 m; NED	+ ve
Biniraj et al. [9]	38	F	Upper Left posterior alveolar ridge	3 4	2 m	6 m; recurrence and death	- ve
Rahman et al. [35]	36	F	Upper left jaw	7 4.5 3	1 m	1.5 yrs; NED	NA
Lazaridou et al. [6]	75	F	Left buccal area and maxillary sinus	-	6 m	1 yr; NED	NA
Adachi et al. [14]	42	M	Mandible	-	-	2 yrs; NED	???
Naresh et al. [36]	70	F	Gingiva	3 4	6 m		+ ve
Case 1	13	F	Maxilla	2 1.3 0.3	unknown	NA	+ ve
Case 2	27	M	Retromolar pad	2 1.4 1.4	3 weeks	NA	- ve

Table 1: Review of clinical features of the reported cases including ALK-1 positivity of oral inflammatory myofibroblastic tumors.

Case 2

A 27 year old male presented with a 3 2 cm exophytic hemorrhagic pedunculated soft tissue lesion of three weeks duration on the retromolar pad. The lesion was tender but showed no bony involvement. The clinical differential diagnosis included benign lesions like pyogenic granuloma, peripheral giant cell granuloma and focal fibrous hyperplasia. Microscopic examination showed an ulcerated epithelium overlying fibromyxoid to fibrous connective tissue stroma. The mass of proliferative spindle cells showed ovoid to spindle nuclei with abundant eosinophilic cytoplasm. A moderate inflammatory component consisting of chiefly neutrophils, occasional lymphocytes and giant cells was noted in the stroma. Immunohistochemical stains for alpha-1 antitrypsin and vimentin were positive whereas cytokeratin, smooth muscle actin and S100 protein were negative. The diagnosis was suggestive of an inflammatory myofibroblastic tumor (Photograph). The Fluorescence in situ hybridization study in 2015 demonstrated no ALK (2p23) rearrangement. The final diagnosis was made on the basis of microscopic examination and immunohistochemical stains. Radical surgery was performed and there is no evidence of recurrence of this lesion in our archival material [4].

Discussion

OIMT is considered to be a benign neoplasm which is infiltrative and locally destructive. Of late its benign nature has been a controversial issue owing to its high recurrence rate, regional metastasis and chromosomal abnormalities [5]. The etiology and pathogenesis are obscure. Theories of its origin range from infectious, autoimmune, traumatic or neoplastic. Current theory supports the immune origin and proposes that the lesion results from the host reaction to stimuli such as trauma, foreign body microorganisms or neoplastic tissues [6]. Until 1998 IMT was considered as a reactive lesion and were known as inflammatory pseudotumor [7]. Based on the cytogenic studies demonstrating clonal genetic alteration and chromosomal abnormalities in approximately 50% of cases, it is considered a true neoplasm and the term IMT has been reserved for the neoplastic lesion [8]. Of the thirty two oral lesions reported in literature since 1981, only one case showed sarcomatous changes, recurrence and ultimately death [9].

OIMTs have been reported in all age groups with the majority of cases arising in adolescence and young adults. This finding was consistent in our cases as well. The ages ranged from 2-82 years. A slight female predilection has been noted. Clinically, it presents as an asymptomatic, firm, and indurated soft tissue mass without any significant systemic signs and symptoms. Intraoral soft tissue sites include the buccal mucosa, tongue, retromolar area, palate, and floor of the mouth. Our soft tissue case was also on the retromolar pad. Depending on the location, the clinical differential diagnoses for soft tissue lesion vary from pyogenic granuloma, fibroma, peripheral ossifying fibroma, peripheral giant cell lesion, squamous cell carcinoma, and metastatic lesions. Intraosseous lesions are rare. Of the 32 oral cases, only 8 were intraosseous. Of these, 5 were in the mandible and 3 in the maxilla. Posterior maxilla was the site of origin in our case. Plain radiographic image of the intraosseous lesion present as asymptomatic, unilocular, ill-defined, expansile radiolucency capable of causing root resorption, suggesting an aggressive lesion [5,9-15]. A similar finding was found in our intraosseous case. CT and MRI images show a space occupying mass with erosion of the involved bone, also suggesting an aggressive lesion. The radiographic differential diagnosis includes an inflammatory, malignant or metastatic lesion. A slow or a rapid increase in size of both the soft tissue and intraosseous lesion has been reported [16].

Histologically, OIMT is composed of spindle shaped myofibroblastic cells interspersed with a variable number of acute and chronic inflammatory cells in a myxoid or collagenous stroma [17], findings consistent in our cases. Myofibroblasts are arranged in a story form and fascicular patterns, have an acidophilus-stained cytoplasm and a round or elliptical shaped plump nuclei and a small nucleoli. Prominent vasculature is evident. Atypical mitosis is rare and necrosis is not seen. Occasionally focal stromal calcification and occasional intravascular emboli of IMT may be seen. These features are of no clinical consequence [16]. Histopathologic differential diagnosis

includes spindle cell neoplasms such as nodular fasciitis, solitary fibrous tumor, benign fibrous histiocytoma, calcifying fibrous tumor, myofibroma, fibrosarcoma, and leiomyosarcoma.

Due to the vast number of lesions mimicking OMIT histopathologically, immunohistochemical analysis aids to confirm the myofibroblastic phenotype of the tumor cells, which are typically reactive for vimentin, desmin, smooth muscle actin, and muscle specific actin. Smooth muscle actin expression is an important marker as approximately 92% of cases show positivity. Anaplastic lymphoma kinase protein (ALK-1) was originally identified as a protein overexpressed in anaplastic large-cell lymphoma. It has subsequently been shown to be overexpressed in a substantial proportion of inflammatory myofibroblastic tumors of various anatomic locations. Approximately 50% of OMITs are ALK-1 positive. This protein overexpression is a result of ALK gene rearrangements on the short arm of chromosome 2 (2p23). The ALK gene may fuse with the clathrin heavy chain, tropomysin 3 (TPM3-ALK) or tropomysinn 4 (TPM4-ALK). These gene rearrangements are often responsible for the overexpression of ALk-1. Most of other fibroblastic and myofibroblastic tumors are ALK-1 negative. Hence, it appears that ALK-1 is highly specific for IMT, but not 100% sensitive [17,18]. Morphologically, ALK-1 positive tumors are indistinguishable from ALK-1 negative tumors [4]. All these factors indicate several biopsies to reach a diagnosis. The presence of ALK rearrangement is associated with a better prognosis and it may thus be of use in both diagnostic as well as therapeutic purposes.

The addition of two cases from our laboratory confirms the difficulty in diagnosing OIMT. Case 1 showed features of an aggressive bony lesion while case 2 appeared like a benign soft tissue lesion. Both lesions were noted in patients younger than 30 years. ALK positivity was 50% in our cases as per the literature.

Treatment

The vast majority of OMIT behave in a benign fashion with rare recurrences. Of all the oral cases reported in literature, only one case recurred resulting in death. Radical local excision is the treatment of choice [18]. Other treatment modalities include steroid therapy, curettage, radiation therapy and chemotherapy. ALK molecular-targeted therapeutic drug crizotinib has been applied in some patients [16]. Because of the unpredictable nature of the lesion long term therapy is mandatory. Though rare, spontaneous regression has also been reported.

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