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Diagnostic challenge in Inflammatory Myofibroblastic Tumor: Case Report

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Inflammatory myofibroblastic tumor (IMT) is a rarely described tumor of unknown etiology and pathogenesis. It occurs primarily in the lungs, but has occurred in other extra-pulmonary sites. Histologically these lesions appear as an inflammatory infiltrate within a variably myofibrotic background. Current evidence shows that inflammatory myofibroblastic tumors are neoplastic processes resulting from chromosomal translocations that often cause an overexpression of ALK kinase, which is often assessed using immunohistochemical studies. Currently, the biological behavior of oral inflammatory myofibroblastic tumor is still uncertain. This article describes the clinical, histological, and operative features of a case of IMT of the Mandible. I report such a case of inflammatory myofibroblastic tumor of the mandible in a 16-year-old girl. The patient presented with a large aggressive ulcerative soft tissue mass of 3 year duration in the rigth mandibular molar gingiva. Histologically, section show; loosely arranged myofibroblasts in an edematous and myxoid background with plasma cells, lymphocytes, eosinophils, and blood vessels and overlined by ulcerative skin, no necrosis or mitosis. Immunohistochemically, the fibroblastic or myofibroblastic spindle cells were positive for vimentin, α-smooth muscle actin, and Ki-67 (MIB-1) but negative for desmin, pan-cytokeratin, S-100 protein, CD34, CD68, CD99, bcl-2, β-catenin, estrogen receptor, progesterone receptor. These spindle cells were focally and weakly Ki-67- (MIB-1-) positive. A pathological diagnosis of inflammatory myofibroblastic tumor was made. The postoperative course was uneventful, and the patient has had no recurrence in the 1 year follow-up period. Although no evidence of oral inflammatory myofibroblastic tumor recurrence or malignant transformation has been reported, it has been observed that in inflammatory myofibroblastic tumors of other regions, a prolonged follow-up is necessary after surgical resection.

Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare entity included in a heterogeneous group of spindle cell proliferations, which encompasses a broad phenotypic and biologic spectrum of diseases ranging from reactive lesions to benign neoplasms[1]. It was first observed in the lung and described by Brunn in 1939 and was so named by Umiker in 1954 because of its clinical and radiological behavior that mimics a malignant process[2]. The most common sites of involvement include the lung, liver and orbit, but it has been reported to occur in nearly every site of the body, including the major salivary glands and the oral cavity[2, 3]. It was called inflammatory pseudotumor (IPT) until 1998 when the term inflammatory myofibroblastic tumor (IMT) was proposed as being a more descriptive name[1]. The terms "inflammatory pseudotumor" and "inflammatory myofibroblastic tumor" were used synonymously in most publications, all 22 cases diagnosed in the English literature as IPT or IMT (Based on criteria followed by Brooks *et al*. 2004). The most common intraoral site observed was the buccal mucosa, with lesions occurring over a wide age range 2 to 82 years with a mean of 32 years and showing a 1.6:1 female predilection. The lesion typically presents as a firm, indurated swelling and does not produce significant systemic symptoms, unlike its counterpart in visceral organs[4.5]. Intrabony presentation of IMT is rare. Only three cases have been reported[6-8] .

The purpose of this study is primarily to present a case of IMT in the mandible, describing its clinical aspect, immunophenotype and management, showing for the first time myofibroblastic fibronectin expression contributing to the knowledge and characterization of this entity. Treatment of IMT should entail complete surgical resection[4,12] and since IMT may present a low-grade malignancy, longer follow-up is needed[13]. Extrapulmonary IMTs seem to exhibit a more favorable clinical course and treatment outcome, evolving with lower rates of recurrence, malignant transformation, metastasis, and mortality.

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Case report

A 16-year-old woman presented for evaluation of a painless swelling with a three-year history of progressive growing on the right side of the mandible (Figure 1). Her medical and surgical histories were unremarkable, and she denied any previous lesions or local trauma. Intraoral examination revealed a 10 cm reddish exophytic mass extending to the oropharynx pushing the tongue laterally, with a rubbery consistency, attached to the mucosa (Figure 2). The overlying mucosa presented ulcerated areas with no discharge. On the basis of the clinical findings, glandular neoplasm, non-neoplastic proliferative process or malignant tumour were considered as differential diagnosis. Imaging studies were performed Plain film radiography of the postero-anterior view of mandible revealed destruction of the right mandible and one impacted molar tooth on the right proximal part of the ascending ramus (Figure 3).

An incisional biopsy was performed and, microscopic examination revealed an ulcerated nodular mass composed of proliferating spindle cells in a predominantly myxoid stroma admixed with a variable amount of acute and chronic inflammatory cells along with a rich vascular network (Figure 5). Towards the periphery, the lesion was more cellular with a focal fascicular arrangement of the spindle cells. In all fields, an inflammatory component was prominent and was formed mainly by neutrophil and lymphocytes with a few plasma cells, histiocytes and eosinophils. The spindle cells exhibited plump tapering vesicular nuclei and were haphazardly arranged. Non-cohesive larger stellate or polygonal cells with ovoid vesicular nuclei and prominent nucleoli were scattered. Nuclear atypia and mitosis were not evident.

In addition, immunohistochemistry was performed with proliferating spindle cells showing intense and diffuse positivity for vimentin (M0725, DakoCytomation, Carpinteria, CA, USA), smooth muscle actin (SMA;M0851, DakoCytomation) and muscle specific actin (HHF-35; M0635, DakoCytomation) . The immunostaining for desmin, however, was negative as were also negative reactions to AE1/AE3 (M3515, DakoCytomation), S-100 (Z311, DakoCytomation), CD68 (M0814, DakoCytomation), MyoD1 (M3512, DakoCytomation), and caldesmon (M3557, DakoCytomation). In an attempt to delineate the potential neoplastic nature of this lesion, we assessed the immunohistochemical expression of ALK protein (M7195, DakoCytomation), although none reactivity was found. A diagnosis of IMT was established. Furthermore, fibronectin (A0245, DakoCytomation) immunostaining was performed, showing strong positivity in spindle cells, corroborating with a myofibroblastic phenotype.

On surgical procedure Prophylactic tracheotomy done for intubation as well as for post operative air way management and all aseptic precautions, tumor mass was exposed externally. After extraction of left lower first premolar, osteotomy cut was placed and completed lingually and buccally and right side hemimandibuloectomy with disarticulation done.

The tumor mass was removed along with bone margin of 1.5 cm (Figures 4 and 6). Hemostasis was achieved, vacuum drain was secured and closure was done in layers. Antibiotics, analgesics and anti-inflammatory drugs were given postoperatively

The wounds healed unevenly and sutures were removed on 7th postoperative day. Patient has been kept under periodic follow up since then. No recurrence had been reported by the time of presenting this article. The patient was satisfied with her quality of life and remained disease free the time of her last follow-up, 1 year after surgery (Figure 7).

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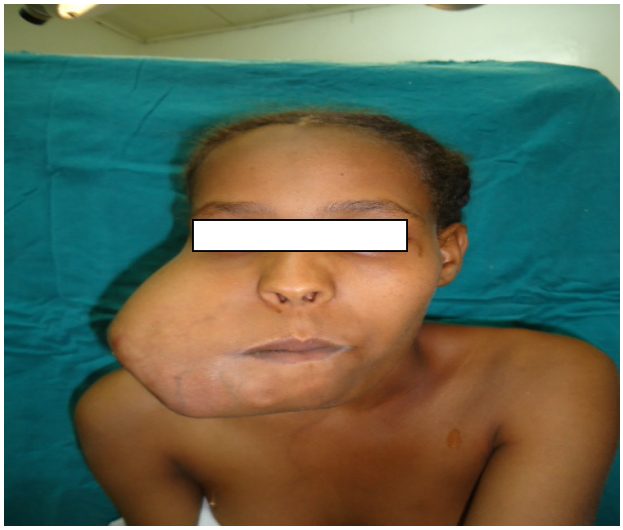

Figure 1. Clinical View of the Mandible Showing Right side laterally Expanded Round Mass.

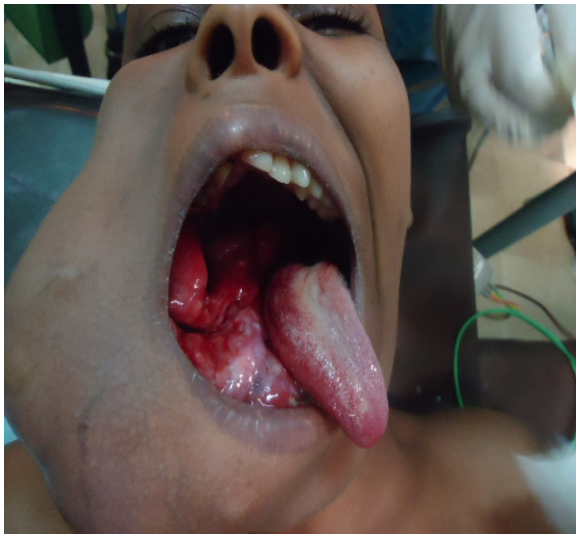

Figure 2. Shows the Intra Oral view with the Tongue Pushed Laterally by the Mass

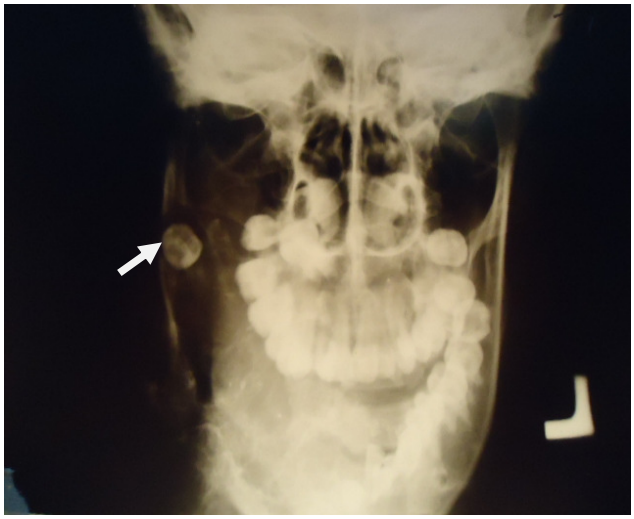

Figure 3. PA View of Mandible Showing Gross Destruction of Right Body and Ramus of the Mandible with Flecks of Bone within the Lesion and One Impacted Molar Tooth at the Proximal Part of Ascending Ramus (Arrow).

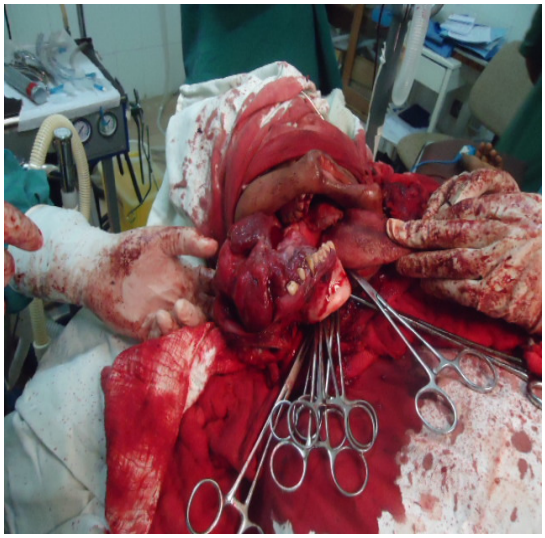

Figure 4. Trans-operative Aspect of the Inflammatory Myofibroblastic Tumor during Surgical Excision

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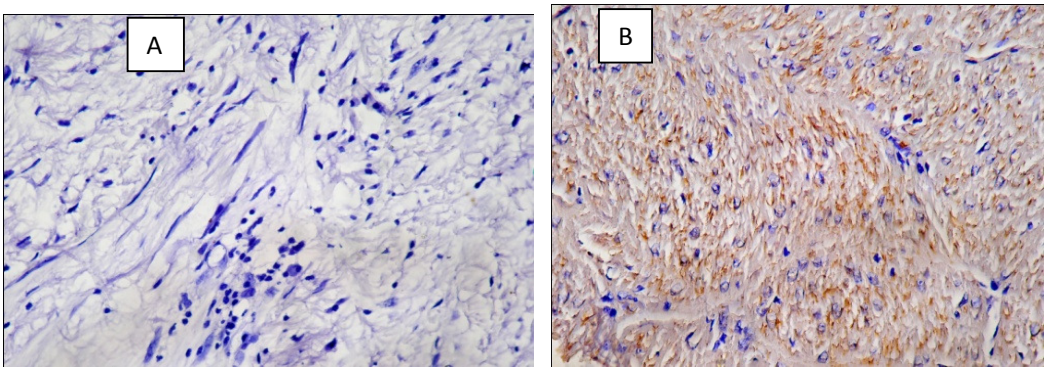

Figure 5. Photomicrographs of Inflammatory myofibroblastic tumor. A: Spindle Tumor Cells Scattered in a Loosely and Myxoid Background with Inflammatory Proliferation; in detail, myofibroblasts and eosinophils (hematoxylin and eosin stain). B: Immunohistochemical Staining of SMA in Spindled Myofibroblasts.

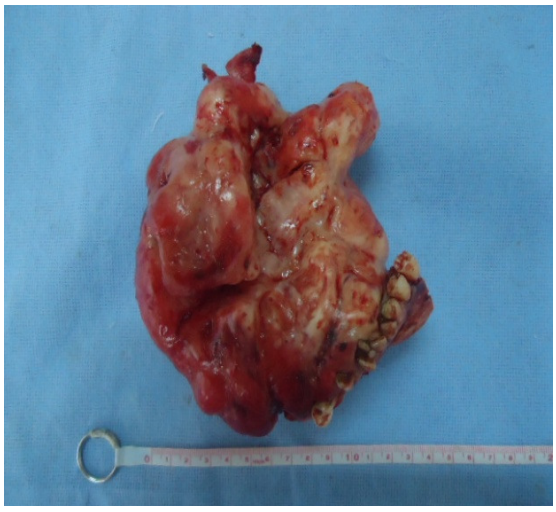

Figure 6. Excised Tumor with Size of 14 cm Anterioposthericly and 16 cm Superioinferiorly

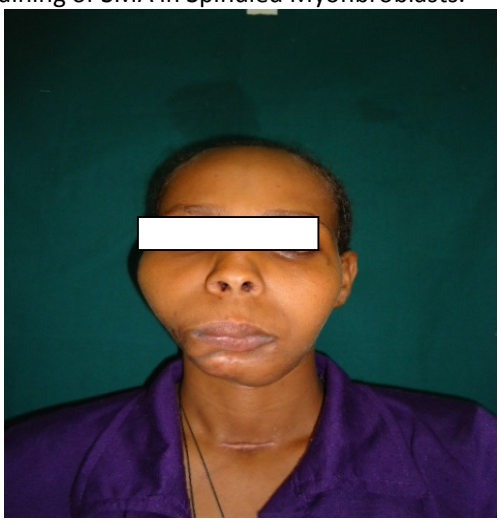

Figure 7. Postoperative Appearance with Minimal Facial Disfigurement

Discussion

Oral IMT is a very rare lesion which along with its nonspecific clinical appearance may pose difficulties to diagnosis and management. Its rapid growth rate may simulate a malignant disorder and therefore warrants a comprehensive histopathological assessment[12]. Originally reported in the lung, extra-pulmonary IMTs have been described[1], including head and neck region[4] mainly in the aerodigestive tract, major salivary glands and soft tissues of the neck[1,14,15]. A limited number of patients with oral IMT have been reported[12], thus contributing with the unspecified pattern of clinical aspects and clues to diagnosis. In the oral mucosa, the most reported sites of occurrence are submandibular region[16], parotid duct[14], retromolar area[17], alveolar mucosa of the molar region[12], tongue[13], maxilla[14] and the hard palate[4]. Typically, oral IMTs have been described as a well circumscribed, solitary nodule or mass, frequently pedunculated, and rubbery consistency, as the present one, have been reported[14]. The etiology of most oral IMTs remains controversial. Some authors widely consider it a benign neoplastic lesion[4], and others support a reactive etiology[17], since the rapid growth and subsequent indolent behavior of most oral IMT are similar to that of many common reactive oral lesions[12].

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Differently, in other sites, this condition can behave in a more aggressive or even malignant way[13], constituting a true neoplastic process due to the potential for local recurrence, development of multifocal tumors, infiltrative local growth, and even distant metastasis[6]. Histologically, various aspects can be seen. In the current case one of the patterns was observed; loosely arranged myofibroblasts in an edematous and myxoid background with plasma cells, lymphocytes, eosinophils, and blood vessels[12,17]. A second configuration that can occur is distinguished by the presence of dense aggregates of spindle cells arranged in a variable myxoid or collagenized background, admixed with a distinctive inflammatory infiltrate[18]. Finally, a third pattern of IMT is characterized by prominent collagen sheets, resembling scar tissue, with scattered plasma cells and eosinophils[12]. Cytological atypia with nuclear pleomorphism and increased mitotic activity are uncommon features[4,12], and may be associated with malignant transformation[12]. Immunoprofile is helpful in the establishment of the diagnosis of IMT especially by the identification of myofibroblasts. The myofibroblast is becoming recognized as a target for translational medicine, since it appears as a significant cellular participant in granulation tissue and several other human diseases[12]. Previously, the characterization of the fully differentiated myofibroblast immunophenotype included positivity to vimentin and α-smooth-muscle actin, and negativity to smoothmuscle myosin and usually desmin[11]. However, a spindle cell positive to SMA is an imprecise definition for the myofibroblast since a number of normal cells also express it[19].

In addition, lesions first regarded as myofibroblastic are shown to vary in their level of differentiation, and some appear to be smooth-muscle rather than myofibroblastic[10]. Desmin negativity rather than positivity should be seen as a more appropriate indicator of myofibroblastic differentiation[19]. Finally, as recently suggested, the main characteristics of the myofibroblast include a spindled or stellate morphology, immunostaining for alpha-smooth-muscle actin and the extra domain A variant of cellular fibronectin, and an ultrastructure of rough endoplasmic reticulum, peripheral contractile filaments and the cell-to-matrix junction known as the fibronexus, being important for maximum diagnostic confidence in some myofibroblastic lesions[10].

The immunophenotype of the IMT presented herein is in accordance with the identification of a myofibroblast [10,19] and also by other IMT reports[12,18] with strong diffuse cytoplasmic reactivity to vimentin, SMA and HHF-35 in a focal or diffuse pattern and also negativity to desmin, although the latest could be identified in many cases, as well as focal cytokeratin immunoreactivity[20]. Myogenin, myoglobin, and S-100 protein are also negative[1] as were in the present case. Furthermore, we believe that more investigations on tumor behavior should take into account the fibronectin immunoprofile, since it is known that this protein shows properties that could precipitate a cascade leading to a number of cellular activities, such as differentiation, migration, mitosis all important to tumor progression[19]. Recently, this marker has been associated to the invasive phenotype of oral carcinoma cell lines, although the authors could not establish if the presence of its expression is an associated phenomena or a causative agent in the invasive process[9]. Immunohistochemical cytoplasmic positivity for ALK (Anaplastic lymphoma kinase) is linked to neoplastic transformation since it provides strong evidence for an oncogenic activating mechanism[12]. Thus, at least a proportion of IMTs presenting ALK genetic alterations are genuine neoplasms[20]. However, ALK expression has been detected in approximately 50% of IMTs, and therefore shows not to be a specific marker for this lesion[1,20]. The present case did not demonstrate immunoreactivity for ALK, as shown by most of the oral cases reported in the literature with only a few reports of oral IMT ALK-positive [12,18]. Whether ALK-positive IMTs represent distinct clinicopathological entities, with different therapeutic and prognostic implications, warrants further investigation[18] in order to clarify the contribution of ALK deregulation to the pathogenesis of oral IMT[12]. In addition to the controversy regarding the biologic nature of IMT, proliferating spindle cells may mimic a sarcoma, potentially leading to a diagnostic dilemma[18].

Various benign and malignant spindle cell proliferations should be included in the differential histological diagnosis scheme of oral IMT such as proliferative fasciitis, nodular fasciitis, infantile fibromatosis,

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myofibromatosis, Rosai-Dorfman disease, fibrous histiocytoma, solitary fibrous tumor, follicular dendritic cell tumor, low-grade myofibroblastic sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, and spindle cell carcinoma[9,17]. So, the knowledge of the different histological patterns of IMT, identification of a predominant inflammatory component and immunohistochemical study allow distinction between these entities, being helpful to the accurate diagnosis[12], as emphasized by the present report, and also preventing a more aggressive surgical procedure. Management of IMT should entail complete surgical resection[4,12], and since IMT may present a low-grade malignancy, longer follow-up is need[13]. Extrapulmonary IMTs seem to exhibit a more favorable clinical course and treatment outcome, evolving with lower rates of recurrence, malignant transformation, metastasis, and mortality[12]. One noteworthy feature is that oral IMT seems to behave differently from IMT occurring elsewhere in body[13], displaying variable local recurrence and not reported metastasis[4]. There may be a need to recognize it as a separate entity. The diversity of IMTs microscopic appearance and the lack of correlation between these variables and the clinical evolution of these tumors to date, encourage further research on biomarkers, such as fibronectin, that might provide guidelines to tumor progression, treatment and prognosis.

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