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Case Report

Diagnostic Dilemma in Oral Inflammatory Myofibroblastic Tumor: A Case Report with Special Emphasis on Clinical and Histopathological Mimics

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Abstract

An exophytic pedunculated or sessile growth in the oral cavity is most often encountered in routine practice. Occasionally, few exophytic growths sharing clinical presentation of reactive lesions have mixed characteristics of different pathological patterns in histopathology and thus create a diagnostic dilemma for the clinician. We present a case of 34-year-old female who had a pedunculated growth in the upper anterior gingiva, mimicking clinically pyogenic granuloma. After surgical excision and procedural, histopathological, and immunohistochemical evaluation, the lesion was diagnosed as inflammatory myofibroblastic tumor (IMT). Few cases have been reported in the literature of oral IMT but the exact clinical behavior, and etiopathogenesis of these oral lesions have not been extensively studied. IMT is an uncommon tumor of the oral cavity even though it is seen in other parts of the body. Hence, IMT should be considered in the differential diagnosis of oral tumors.

Key words: Inflammatory myofibroblastic tumor, Inflammatory pseudotumors, Oral exophytic lesions, Spindle cell lesions

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is an unusual lesion generally occurring in the visceral tissues of children and adults and has been diagnosed in different regions of the body, such as the larynx, bone, and central nervous system.[1] However, it is rarely noted in the head-and-neck region.[2] Sometimes, these lesions can also occur in older adults. Earlier it was included within the category of inflammatory pseudotumors. At present, it has come forth as a distinctive entity due to its characteristic clinical, histopathological, and molecular presentations. This mesenchymal lesion rarely metastasizes but tends to recur and may be multicentric. Moreover, it is commonly associated with frequent clonal alterations, involving chromosome 2p which also supports its neoplastic nature. IMT has been classified as a neoplasm of intermediate biological potential by the recent World Health Organization (WHO) classification of tumors. Histologically, it is composed of a varied pattern of myofibroblastic spindle cell proliferation (in fascicles and storiform pattern) along with varying amounts of inflammatory cell infiltrate chiefly lymphocytes and plasma cells and occasionally, neutrophils and eosinophils. Calcifications hemorrhage and necrosis have also been observed in some cases.[1] Approximately, 50% of these tumors show gene alteration of anaplastic lymphoma kinase (ALK) which is a tyrosine kinase receptor located on chromosome 2 resulting in tyrosine kinase activation. These neoplasms are positive for ALK protein by immunohistochemistry. However, ALK-negative IMTs have also been reported which may have other molecular aberrations that need further investigations.[3] Although oral cases have not been reported much in the literature, IMT can occur within the oral cavity, presenting either as gingival mass or intrabony growth. Hence, this entity must be excluded while dealing with any spindle cell tumor in the head–neck region.

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CASE REPORT

A 34-year-old woman reported to the oral pathology department for routine histopathological evaluation after

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surgical excision of a pedunculated growth in between upper anterior teeth. As per the surgical note, the lesion was symptomless, slow growing, non-bleeding, present over a period of 6 months, and measured 2–2.5 cm in size. Her medical history was non-consistent and she was not under any routine medication. Social history was also non-contributing with no oral habits. Intraoral periapical radiograph revealed patchy radiolucent areas with indistinct margins [Figure 1]. Primary healing of the lesion was satisfactory after 7 days, with areas of erythema observed on both labial and palatal gingiva of upper central incisors, as shown in the picture [Figure 2].

Histopathological evaluation revealed the presence of highly cellular connective tissue stroma and covered with parakeratinized stratified squamous epithelium, atrophic at places, and hyperplasic at other areas. The presences of lymphoplasmacytic inflammatory cells were observed which were diffusely arranged and interspersed within strands of collagen fibers with plump fibroblasts. At areas, myxoid stroma was also noted with irregular trabeculae of degenerated bone. In some areas, spindle-shaped cells with long cytoplasmic processes were present in haphazard storiform patterns [Figures 3 and 4].

Immunohistochemical analysis revealed a 'tram track' like staining pattern for alpha smooth muscle actin (SMA) of the tumor cells [Figure 5] but negative for ALK [Figure 6]. The histopathological diagnosis was given as an IMT.

DISCUSSION

IMT is an uncommon, intermediate-grade mesenchymal neoplasm comprising fascicles of myofibroblasts intermixed with inflammatory cells.[4] Earlier IMT was included within the group of inflammatory pseudotumors (IPTs),[1] developing as a result of chronic infection, tissue damage, or reaction to the foreign body.[2] IPT is a broad term that includes both reactive and neoplastic

Figure 1: Radiograph showing patchy radiolucent areas with indistinct margins

Figure 2: Post-operative photograph of the patient

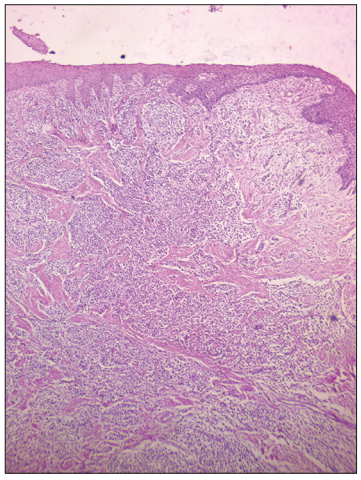

Figure 3: Photomicrograph of H&E-stained sections showing haphazard storiform arrangement (×10)

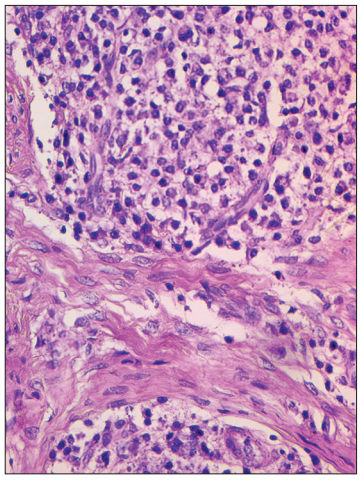

Figure 4: Photomicrograph of H&E-stained sections showing spindle-shaped cells (×40)

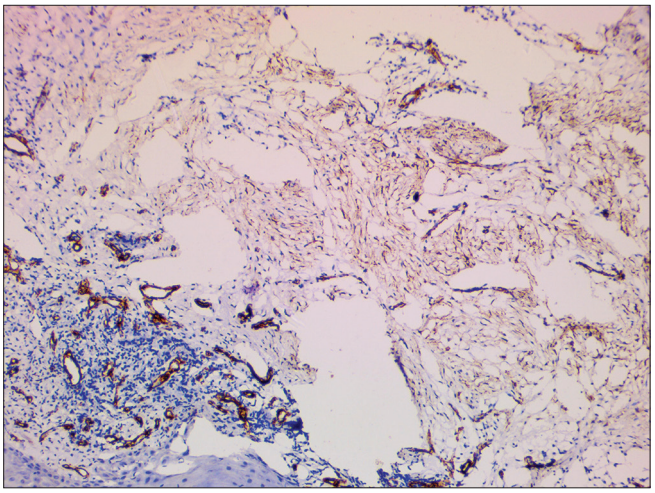

Figure 5: Photomicrograph of immunohistochemistry showing positivity of smooth muscle actin

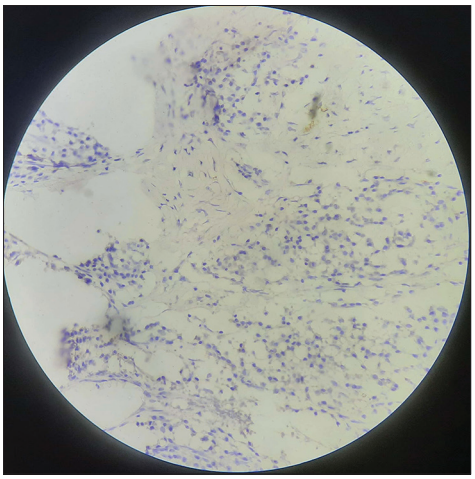

Figure 6: Photomicrograph of immunohistochemistry showing anaplastic lymphoma kinase-negative cells

lesions having similar histologic features of spindle cell proliferation along with inflammatory cell infiltrate. Besides IMT, the other lesions included within IPTs are pseudosarcomatous myofibroblastic proliferations of the genitourinary tract, infective and reparative diseases, and IPT of lymph nodes spleen and orbit.[1]

IMT in the last two decades has emerged as a separate entity from within the broad category of IPT due to its characteristic clinical, histologic, and molecular attributes.[1] This lesion in the past was also termed as atypical fibromyxoid tumors, pseudosarcomatous fibromyxoid tumors, plasma cell granulomas, pseudosarcomatous myofibrotic proliferations, post-operative spindle cell nodules, and IPT.[4]

Previously as IPTs and IMTs were used synonymously, it was thought to arise as an immunologic response to microorganisms, tissue damage, foreign body, or a neoplastic process.[5] In addition to these factors, some researchers stated that smoking may also be responsible for the development of such lesions.[6] The different viruses that have been associated with this lesion are Epstein–Barr virus and human herpesvirus 8. A possible relation between IMT and immunoglobulin G4-related disease has also been hypothesized.[5] The other bacterial microbes linked to this disease are actinomycetes, *Nocardiae*, *Bacteroides*, *Campylobacter*, *Coxiella*, *Eikenella*, *Klebsiella*, and *Pseudomonas*.[7] However, most of these cases were not true IMTs. The exact etiology or predisposing factor in the present case was not evident.

The etiopathogenesis of IMT per se is still uncertain. In about half of the IMTs, there is a rearrangement in the ALK locus present in the short arm of chromosome 2 (2p23), leading to the formation of a fusion oncogene. This clonal chromosomal derangement results in abnormal regulation of the ALK gene with activation of the ALK receptor which is a tyrosine kinase receptor and, therefore, cell proliferation by abnormal phosphorylation of cellular substrates. Such alteration has been described in both pulmonary and extrapulmonary IMTs.[1] There are various fusion partners of the ALK gene in IMT. These are TPM3 at 1p23, TPM4 at 19p13, ATIC at 2q35, CLTC at 17q23, CARS at 11p15, RANBP2 at 2q13, SEC31L1 at 4q21, and FN1.[8] Hornick *et al.* reported the rearrangement of another tyrosine kinase gene (ROS1) located at 6q22, in a group of ALK-negative IMTs resulting in fusion between YWHAE-ROS1 or TFG-ROS1 genes.[3] Although there is a clonal proliferation of the myofibroblasts, the inflammatory cells chiefly the plasma cells are polyclonal.[1]

Most commonly it develops in the lungs, abdomen–pelvic region, and in retroperitoneum.[1] Among the extrapulmonary location, it has been observed in the liver, uterus, genitourinary tract, and head-and-neck region. Head-and-neck IMTs make about 5% of all IMT and 14–18% of all extrapulmonary lesions.[2] In the head-and-neck region, the orbit is a common site of occurrence. In addition to orbit, it has been reported in the parapharyngeal spaces, maxillary sinus, epiglottis, major salivary glands, and oral cavity. In the oral cavity, the different sites of involvement are the gingiva, tongue, buccal mucosa, hard palate, mandible, and submandibular salivary gland.[7] Hence, 28 cases of oral IMT have been reported in the literature.[9] The lesion in our case developed in the maxillary gingival region.

In general, this tumor usually occurs in children and adolescents but may arise at any age even as late as the 8th decade of life.[1] Even oral cavity tumors may occur at any age ranging from 2 to 82 years;[9] with a mean age of 32 years.[8] It is more common in females than males.

IMT of the oral cavity also has a female predilection (5:4 according to Shetty *et al.* 2018 and 1.6:1 according to Binmadi *et al.* 2011), as was the present case.

Most IMTs of the oral cavity appear as a well-circumscribed painless slowly growing mass of varying size and may be sessile or pedunculated with no history of bleeding or discharge of exudates.[7,8] It may cause erosion of the underlying bone. Other common benign entities, such as pyogenic granuloma, peripheral ossifying fibroma, peripheral giant cell granuloma, and peripheral odontogenic tumor variants, may show similar presentations. In the present case, the tumor also showed the above clinical and radiological behaviors, with a clinical provisional diagnosis as pyogenic granuloma.

Histology of IMT under H&E stain appears as a mixture of spindle cells and chronic inflammatory cells in a myxoid to collagenous stroma. The cellularity of the spindle cells is variable and is composed of a heterogeneous group of myofibroblasts and fibroblasts. The inflammatory cells are chiefly plasma cells and lymphocytes but eosinophils and neutrophils may also be observed. The spindle cells are arranged in a fascicular or short storiform pattern, which are rather uniform in appearance having pale eosinophilic cytoplasm with ovoid or tapering vesicular nuclei and one or more small nucleoli.[1] Sometimes, there may be mild nuclear pleomorphism but there is not much mitosis. Hypercellularity, necrosis, atypical mitosis, and the presence of large ganglion cells are some of the aberrant features that are rare and infrequent.[1,7]

Three basic histological patterns have been explained by Coffin *et al.* and it can occur in different combinations in the same tumor. This classification is now universally accepted.

(1) Myxoid/vascular, (2) Compact spindle cell, and (3) Hypocellular fibrous patterns.[7,10]

1. The myxoid/vascular pattern is composed of loosely arranged plump spindle cells present in a myxoid or edematous stroma having well-formed blood vessels. The inflammatory infiltrate consists of more neutrophils and eosinophils and less of plasma cells. This histological picture must be differentiated from nodular fasciitis and other spindle cell lesions.
2. The distinctive feature of compact spindle cell patterns is the proliferation of spindle cells which are arranged in a fascicular or storiform pattern within a collagenous stroma. It resembles fibrous histiocytoma. There are numerous plasma cells. Distinct lymphoid follicles and plasma cell aggregates can also occur.
3. The hypocellular pattern which is also known as the fibromatosis-like pattern consists of elongated instead of plump spindle cells and the stroma is highly collagenous and thus resembles desmoid tumor or scar tissue and calcifying fibrous tumor. There are scattered lymphocytes, plasma cells, and eosinophils. Foci of dystrophic calcification and metaplastic bone may be noted within the highly collagenous stroma.

The case under discussion showed a second type, i.e., compact histological pattern. Considering the histological differential diagnoses, this compact spindle cell pattern should be differentiated from solitary fibrous tumors and benign fibrous histiocytomas. The solitary fibrous tumor has hemangiopericytoma-like areas and strong CD34 staining which is absent in IMT. The spindle cells are arranged haphazardly or in poorly defined fascicles. Benign fibrous histiocytoma comprises fibroblasts arranged in intersecting fascicles, sheets, and characteristic storiform patterns. It also contains foamy histiocytes. This arrangement is not seen in IMT and there is the absence of histiocytes.

IHC plays an important role in diagnosis, especially in the identification of myofibroblasts.[7] Approximately 50% of these tumors show gene alteration of ALK which is a tyrosine kinase receptor located on chromosome 2, resulting in tyrosine kinase activation. These neoplasms are positive for ALK protein by immunohistochemistry. However, ALK-negative IMTs have also been reported, which may have other molecular aberrations that need further investigation.[3] In the present case, the tumor cells showed positivity for SMA, but negative for ALK.

IMTs are tumors of unpredictable clinical behavior. WHO has classified these as tumors of intermediate biological potential due to the tendency of local recurrence and a small risk of distant metastasis.[1] These require complete surgical excision and continuous monitoring of clinical consequences.[11] The patient in the present case did not report any complication or recurrence in 1-year follow-up.

CONCLUSION

IMT is a diagnosis by exclusion, distinguished primarily by the histological findings of marked spindle cell populations in a varied background and arrangements. Immunohistochemistry plays an important role for accurate diagnosis. Awareness of oral IMT and its distinctive morphologic and microscopic features is important in avoiding misdiagnosis. It is also important to recognize this entity as a benign inflammatory lesion to avoid unnecessarily extensive and radical surgery. This report reinforces the existence of IMT in the oral cavity as well as the need for clarification of the unknown nature of IPT.

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