CASE REPORT

Slow-Growing Large Irritation Fibroma of the Anterior Hard Palate: A Case Report Using Immunohistochemical Analysis

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Abstract Irritation fibromas are recognized as fibrous lesions, usually reactive hyperplasias; however, the mechanism of enlargement is unclear. This paper reports on an abnormally large irritation fibroma of extremely gradual growth. The immunohistochemical features (CD34, α -SMA, vimentin, Ki-67, and TGF- α) of this irritation fibroma are presented to distinguish reactive hyperplasia from other true fibrous neoplasm diseases. In the only previous study, it was reported that the expression of TGF- α might be associated with the development of oral fibromas. Therefore, we investigated the relationship between this exceptionally-large fibrous lesion of extremely slow growth and the immunohistochemical reactivity of TGF- α , finding that, in contrast to the previous study, TGF- α was not expressed. This is the first study to evaluate the enlargement mechanism of such a large irritation fibroma using the approach of immunohistochemical analysis, and it indicates that such analysis can help elucidate the diverse causes and enlargement mechanisms of irritation fibromas.

Keywords Irritation fibroma · Hard palate · Immunohistochemistry

Introduction

Fibromas are the most common disease in the oral cavity [1, 2]. However, it is difficult to distinguish between true neoplasms and reactive hyperplasias of fibrous connective tissue [1]. The majority of fibrous diseases in the oral cavity are recognized as reactive hyperplasias in response to local irritation or trauma. The size of fibromas usually remains small, and cases that are >1.0 cm in diameter are rare [3]. There are few documented cases of large irritation fibromas (>4.0 cm) that analyze the mechanism of enlargement. The authors here report a rare case of a large irritation fibroma of the anterior hard palate that had grown over quite a long period of time in a 57-year-old Japanese man, and analyze the nature of the lesion using an immunohistochemical approach [CD34, alpha-smooth muscle actin (α -SMA), vimentin, Ki-67(Mib1), and transforming growth factor-alpha (TGF- α)]. In the only previous study, it was reported that TGF- α is related to fibroblast proliferation in growing fibromas [4]. In this case, though, TGF- α was not expressed, and this immunohistochemical analysis indicated that TGF- α might not have had anything to do with the enlargement of irritation fibroma of extremely slow growth or the unchanging state of the lesion.

Case Report

A 57-year-old Japanese man was referred with the chief complaint of a hard, large mass on the anterior left hard palate that had gradually become enlarged. The patient had first noticed the appearance of a small lesion about 10 years before. The painless lesion had been growing slowly year by year without causing any obstruction to his speech or mastication. The medical history of the patient

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was not a contributing factor, and he was otherwise in good health. There was no history of infection or trauma around his anterior hard palate. An intraoral examination revealed a 4.5-cm, firm, solitary, well-circumscribed nodule without haphalgesia (Fig. 1A). The surface of the lesion was covered with normal mucosa (Fig. 1B). Tooth mobility in this region was not noted. A radiographic examination and an axial computed tomography (CT) scan did not show any tooth root or bone involvement. On T1-weighted and T2-weighted images, the central area of the lesion produced a low intensity signal, while the peripheral area produced a slightly high intensity signal. The signal intensity in the central area of the lesion on both T1 and T2-weighted images was homogenous. The lesion was totally excised under general anaesthesia without complications. In this operation, the surgical procedure was to remove the fibroma in its entirety from the basal part of lesion including that part of the periosteum from which it formed, after marking the bottom of the lesion with binding suture. No recurrence has been observed for over 1 year, as the postoperative photo confirms (Fig. 1C).

A histopathological examination revealed the nodular mass of fibrous connective tissue to be covered by squamous epithelium (Fig. 2A). Scattered mild inflammation was observed beneath the epithelium (Fig. 2B). The connective tissue in the center of lesion comprised dense

collagen fiber (Fig. 2C). Many small blood capillaries were scattered all over the lesion. In individual immunohistochemical stainings, some fibroblasts in the lesion showed positive reactivity for vimentin (Fig. 3A) and negative reactivity for Ki-67, CD-34 and α -SMA (Figs. 3B–D). Positive reactivity cells for TGF- α were not seen in the epithelium and subepithelium areas (Figs. 4A, B). Furthermore, the upper part and under part of the lesion showed negative reactivity. Thus, this lesion was not a true tumor because of the absence of monotonous fibroblast proliferation. Based on these microscopic findings, a diagnosis of irritation fibroma was rendered.

Discussion

The fibroma is the most common lesion in the oral cavity. In our case, it was not so difficult differential diagnosis to suppose one type of fibroma. The several clinical features of this case, for example, firm, solitary, well-circumscribed nodule without haphalgesia, progress of this lesion were consistent with those of fibroma. Also, findings of CT and MRI suggested the layers structure of this fibroma with main central area and thin peripheral area. These radiological findings were not inconsistent with fibroma. However, it is difficult to distinguish between a true

Fig. 1 **A** Intraoral view shows large solitary nodule in the anterior hard palate. **B** Cut section demonstrates fibrous appearance with white and homogenous aspect surrounded by thin epithelium. **C** Postoperative intraoral view shows no recurrence (1 year after the operation)

Fig. 2 **A** The covering epithelium demonstrates rete ridges (hematoxylin-eosin, original magnification $\times 10$). **B** A mild inflammatory reaction is seen beneath the epithelial surface (original magnification

$\times 100$). **C** The stroma is typically dense collagenous fibers (original magnification $\times 100$)

neoplasm and a reactive hyperplasia of fibrous connective tissue. Fibrous lesions such as reactive hyperplasias are classified into several types: irritation fibromas, traumatic fibromas, focal fibrous hyperplasias and fibrous nodules [1]. On the other hand, true fibromas, i.e. solitary fibrous tumors, collagenous fibromas and elastofibromas, are known as neoplastic fibromas. To date, several studies on neoplastic fibromas have been reported [5–10]. However, no previous study has evaluated the enlargement mechanism of large irritation fibromas using the approach of immunohistochemical analysis.

In general, irritation fibromas comprise a nodular mass of fibrous connective tissue covered with stratified squamous epithelium. This connective tissue is extremely dense and collagenized. Therefore, palpation shows that it is very hard. In this case, there was no history of any trauma in the maxilla. The pathological and clinical records of this case accord with the characteristics of the irritation fibroma. Most fibromas are 1.5 cm or less in diameter [1, 3]. In this case, the size is relatively large with the diameter of the lesion being 4.5 cm. It is known that most fibromas are sessile, but in this case it was pedunculated. The basal part of the irritation fibroma was very narrow and small.

The probable cause of this fibroma was some irritation of the left palate mucosa about 10 years before. It was surmised that this incipient small irritation fibroma, after

some further stimulation, slowly became larger under the daily mild influence of chewing and tongue movement over the course of a decade, because the patient had noticed that small lesion about 10 years before. There was no scarring on the surface of the lesion due to the anterior tooth of the lower jaw from the first medical examination to the operation about 3 weeks later. Scattered mild inflammation beneath the epithelial surface in the microscopic images might have been caused mainly by the weak stimulation of the surface of the fibroma through chewing. In addition, the very slow pace of the fibroma's growth was proved by the fact that fibroblasts in the central area of the lesion were immunonegative for Ki-67.

The neoplastic potential of the lesion was low in this case because neither the monotonous proliferation of fibroblasts nor the positive immunohistochemical reactivity of these cells (CD34 and α -SMA) was confirmed. Several cases of true fibromas in the oral mucosa have been reported [10]. The characteristics of a true fibroma are the presence of a capsule and the sharp demarcation of the lesion from the surrounding normal tissue. Moreover, immunohistochemical reactivity is negative for S-100 and SMA [10]. The solitary fibrous tumor is a neoplasm characterized by the proliferation of capillaries surrounded by a mass of round or spindle-shaped cells [5, 6]. Immunohistochemically, the tumor cells were positive for vimentin and CD34, and negative for α -SMA. The

Fig. 3 Immunohistochemical staining patterns. **A** Fibroblasts show positive reactivity for vimentin (original magnification $\times 200$). **B** Connective tissue has negative reactivity for Ki-67 (original magnification $\times 200$). **C** Stroma of connective tissue has negative

reactivity for CD-34 (original magnification $\times 200$). **D** Only vascular smooth muscle cells of small vessels have positive reactivity for alpha-SMA, while other fibroblasts have negative reactivity (original magnification $\times 200$)

Fig. 4 **A** Positive reactivity for TGF- α was not seen in the epithelium and subepithelium areas of the upper side (original magnification $\times 10$). **B** In the bottom area of the fibroma, cells showed negative reactivity for TGF- α

collagenous fibroma, known as desmoplastic fibroblastoma, is composed of stellate or spindle-shaped cells embedded in hypovascular fibrous stroma [7, 8]. Tumor cells were immunopositive for vimentin, and a few cells were positive for α -SMA. The elastofibroma is a degenerative pseudotumor composed of fibrous and elastic tissue associated with frictional irritation or trauma [9]. This elastofibroma is microscopically characterized by a commingling of collagen fibers with coarse elastic fibers demonstrating a scrub-brush or petaloid configuration. However, the above mentioned

features of the true fibroma and neoplastic fibroma differ from the histological and immunohistochemical findings of our case.

In another study on the enlargement of oral fibromas also using the immunohistochemical method, it was suggested that TGF- α might be associated with the development of oral fibromas through an autocrine and/or a paracrine [4]. Scattered inflammation beneath the epithelial surface was observed. In the early phase of inflammation after the irritation to the oral mucosa,

neutrophils and macrophages migrate beneath the epithelium. These macrophages secrete TGF- α in a localized area. Monocytes and neutrophils play an important role in inflammatory reactions, and these cells stored TGF- α in cytoplasmic granules. TGF- α released from macrophages, neutrophils and monocytes in inflammatory reactions could influence fibroblast activity. Therefore, inflammation may induce fibrous hyperplasia.

In our case, mild inflammation was also observed beneath the epithelium; however, immunopositive reactivity for TGF- α was not seen in the basal cell layer of the epithelium. We investigated not only the upper surface area of the fibroma with strong stimulation but also the under surface area with weak stimulation. Both areas showed negative reactivity. Thus, this indicates that negative reactivity for TGF- α may be associated with the extremely slow or steady enlargement of fibromas, as in our case. When an oral irritation fibroma reaches a certain size, the proliferative properties of the lesion may become stable. It has been reported that samples from stable lesions might express TGF- α less than samples from growing lesions in oral fibroma cases [4]. We evaluated the immunohistochemical features of this large-size irritation fibroma and investigated the mechanism of its enlargement. When a fibroma's size is small, it is difficult to detect and judge the type and cause of the fibroma. Fibromas are a very common disease in the oral cavity, so it is necessary to analyze many types of fibromas at all stages in order to elucidate the diverse causes and mechanisms of enlargement of irritation fibromas.

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