Solitary mucosal neuroma in the maxillary incisor gingival papilla without multiple endocrine neoplasia type 2B (MEN 2B): a case report and literature review

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Case Report

Keywords: Solitary mucosal neuroma, Oral neural tumors, Gingival papilla, multiple endocrine neoplasia type 2B, Case report

Posted Date: June 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33744/v1

Abstract

Background

Mucosal neuroma (MN) is a benign neural tumor of peripheral nerves histologically characterized by irregular tortuous bundles of nerve cells with prominent perineurium that lie scattered throughout the submucosa. The tumor is usually associated with the multiple endocrine neoplasia type 2B (MEN 2B) but rarely occurs without the other components of MEN 2B. We present a case of solitary MN without MEN 2B that occurs in the maxillary incisor gingival papilla that has not been reported yet and review the literature.

Case presentation:

A 29-year-old woman presented to our outpatient department with an upper anterior teeth gingiva painless mass for 2-year. Intraoral examination revealed a small, tough, basal wide, well-defined mass in the labial gingival papilla between maxillary central incisor. Excisional biopsy showed that it was characterized by nerve bundles in various sizes surrounded by normal connective tissue in the submucosa under HE staining; Immunohistochemically, the mass showed strongly positive staining of S-100 protein, NSE,NF and weakly positive of EMA. The Laboratory examination and ultrasonography showed no signs of MEN 2B. In the first 6 months of follow-up, there was no evidence of recurrence and other components of MEN 2B. The patient was asymptomatic and she is still being followed up every 6 months. Based on these features, the lesion was finally diagnosed as a solitary gingival MN.

Conclusions

This study showed a rare solitary MN in the gingiva papilla without MEN 2B that has not been reported yet. The histopathological evaluation can be helpful in the differential diagnosis of MN. It is hoped that a greater understanding of solitary MN without MEN 2B in the oral cavity will avoid potential misdiagnosis, and contribute to determining the correct management, which appears to be complete surgical excision with close follow-up for recurrence and other components of MEN 2B surveillance.

Background

In 1975, Khairi et al. [1] proposed that the condition of combined medullary thyroid carcinoma (MTC), pheochromocytomas and mucosal neuroma (MN) should be referred to as multiple endocrine neoplasia (MEN) type 3, also known as multiple endocrine neoplasia type 2B (MEN 2B) now. MEN 2B is an autosomal dominant syndrome associated with RET gene mutations and characterized by an aggressive form of MTC and bilateral pheochromocytomas (PCC) [2, 3]. MN of MEN 2B is always observed on the mucosal surfaces of the lips, tongue, eyelids, and intestines of patients [4], but rarely occur without the other abnormality about MEN 2B. MN without MEN 2B have been reported in the rectosigmoid colon [5], bronchi [6, 7], conjunctiva [8], laryngeal [9, 10, 15], tongue [12–15], lip [13]and hard palate [16], but there has been no reported case in the gingiva to our knowledge.

The solitary MN without MEN that occurs in the gingival papilla is easy to be confused with epulis and other oral neural tumors (ONTs) such as solitary circumscribed neuromas (SCN) in clinical practice. Epulis is an inflammatory reactive tumor-like proliferator with limited growth on the gingiva, especially on the gingival papilla. It is derived from the periodontal ligament and connective tissue of the gingiva. Because it has no tumor biological characteristics and structure, it is a non-genuine tumor, but it is easy to relapse after resection [18]. Solitary circumscribed neuromas

(SCN), also known as Palisaded encapsulated neuroma (PEN), was first reported in 1972 by Reed et al. [19], The oral cavity is the second most frequent location for SCN after the skin, and it most often appears as painless superficial nodule same as MN [20].

Clinically, MN usually presents as a firm, slowly enlarging, small, circumscribed mass, which is painless in most cases [3, 7, 13, 16], although it can frequently cause symptoms such as pain and paresthesia [5, 6, 9, 10, 15]. In the vast majority of cases, complete surgical excision is curative; however, recurrences have been reported in some cases [14, 17]. Histologically, MN is characterized by irregular tortuous bundles of nerve cells with prominent perineurium that lie scattered throughout the submucosa [11, 32].

Herein, we present a case of solitary MN without MEN 2B occurs in the gingival papilla that has not been reported yet.

Case Presentation

A 29-year-old Asian female patient presented to the outpatient clinic of Department of Periodontology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) with a 2-year history of an upper anterior gingiva painless mass accompanied with bleeding on brushing teeth occasionally for several years. She brushes her teeth twice a day for 3 ~ 5 minutes, with the use of dental floss. Her past medical history was noncontributory. Intraoral examination revealed a small, pink-colored, well-defined mass which is tough and basal wide in the labial gingival papilla between maxillary central incisor (teeth nos. 8 and 9) (Fig. 1). At baseline, the patient had poor oral hygiene and gingiva was slightly red and swollen, plaque and calculus deposition, and a small amount of pigmentation was found on the tooth surface; A means probing depth (PD) of 2.83 ± 1.02 mm, means clinical attachment loss (CAL) of 1.18 ± 0.68 mm and 73% of bleeding on probing (BOP). The mandibular left second molar (tooth no. 18) had a full crown restoration with Class II tooth mobility, and the lingual root furcation can be probed horizontally (Class II furcation involvement).

The patient underwent Oral Panoramic Radiography and digital periapical film exam, and the results showed that there were no obvious abnormalities in the imaging performance of the remaining teeth except for tooth no. 18 (Fig. 2a and b). The primary differential diagnoses considered for the gingival mass included peripheral ossifying fibroma (fibrous epulis), fibroma, and other oral benign tumors.

Material And Methods

The patient was informed that periodontal treatment was initiated via oral hygiene instructions and professional supragingival biofilm control, including supragingival and subgingival scaling, 4-6 weeks after periodontal initial therapy, the patient should be re-evaluation, including the mass size and periodontal clinical indexes.

After periodontal initial therapy, excisional biopsy was performed of the mass. The tissue sections were fixed in formalin, embedded in paraffin, and then were stained with hematoxylin-eosin (HE) and immunohistochemistry (IHC). Hematoxylin-eosin staining was performed as follows: The specimen was fixed in 4% paraformaldehyde at 4˚C for 24 h. The specimen was then dehydrated as follows: 70% ethanol (60 min), 80% ethanol (40 min), 95% ethanol (30 min), 100% ethanol (25 min) at room temperature, and embedded in paraffin. Following embedding, the specimen was sliced into 5-μm thick slices. The slides were deparaffinized in xylene, rehydrated in 100% ethanol, 95% ethanol, 80% ethanol and 70% ethanol for 2 min each, and then stained with hematoxylin and eosin for 1 min, all at room temperature. Following heat-induced epitope retrieval, slides were incubated with antibodies specific for S-100 protein, epithelial membrane antigen (EMA), neurofilament protein (NFP), and neuron specific enolase (NSE). To rule out the possibility of MEN 2B, we also did endocrinological examinations and ultrasonography of the thyroid gland.

The literature review was performed using the PubMed electronic database to identify relevant publications before December 2019 using the following search term: “mucosal neuroma without MEN type 2B”. From the publications obtained in this search, those pertaining to cases of NM without MEN type 2B were included in the review. Additionally, a manual search was conducted by cross-referencing the retrieved manuscripts. All available data were reviewed, including epidemiology, clinical presentation, histopathologic examination findings, and surgical intervention (Table 1).

Results

Case presentation

Six weeks after SRP, the re-evaluation clinical data showed a reduction in mean PD (2.67 ± 0.81 mm) and a percentage of BOP (20%). There was no significant change in the size of the mass in the buccal gingival papilla between teeth nos. 8 and 9 (Fig. 2c and d).

Then, we performed an excisional biopsy of the mass. Examination of the biopsy specimen showed a 0.6 cm*0.6 cm*0.5 cm, gray-white colored, well defined mucosal tissue. Histologically, nerve bundles in various sizes surrounded by normal connective tissue in the submucosa can be seen under HE staining, and nerve bundles are wrapped by thick perineurium (Fig. 3a and b).

Immunohistochemically, the mass showed strongly positive staining of S-100 protein, neuron specific enolase (NSE), neurofilament protein (NFP) and weakly positive of epithelial membrane antigen (EMA). (Fig. 4a-h). Based on these features, the pathological diagnosis was MN of the maxillary incisor gingiva. 3 months later, the operation area heals well (Fig. 3c).

To rule out the possibility of MEN 2B, we did endocrinological examinations. The serum concentrations of carcinoembryonic antigen, epinephrine, norepinephrine, dopamine, and calcitonin were all within normal limits. Ultrasonography of the thyroid gland was normal. These examinations showed no signs of MEN 2B. Finally, the lesion was clinically diagnosed as a solitary gingival mucosal neuroma. In the first 6 months of follow-up, there was no evidence of recurrence and other components of MEN 2B. The patient was asymptomatic and she is still being followed up every 6 months.

Literature review

Twelve articles with MN cases without MEN 2B were reviewed [5–10, 12–17]; all articles were published before December 2019. The epidemiology, clinical presentation, surgical treatment, and outcome of this sample population are described in Table 1.

According to the data reviewed, the patients were between 4 and 73 years of age and the lesion had no significant sex predilection. MN without MEN 2B in the oral cavity usually presents as a painless subcutaneous mass. MN in the oropharynx (corner of the mouth, lips, tongue, palate, buccal mucosa and throat) was seen in 12 of 18 cases (66.7%) and a less common location was the bronchia (2/18, 11.9%), conjunctival fornix (1/18, 5.56%), rectosigmoid colon (1/18, 5.56%) and larynx (1/18, 5.56%). Location unknown in one case. No cases of MN without MEN 2B in the gingiva have been reported.

The preferred surgical treatment in the majority of cases was local excision, and 2 cases of recurrence have been reported in previous studies.

Discussion

Oral neurogenic tumors (ONTs) originate from cells associated with components of the peripheral nervous system. As an ONT, mucosal neuroma (MN) can be distinguished histologically from other ONTs such as neurofibroma, neurilemmoma and Palisaded encapsulated neuroma (PEN). Briefly, the microscopic examination of the MN shows nerve bundles in various sizes surrounded by normal connective tissue, and nerve bundles are wrapped by thick nerve bundle membrane, which is not usually seen in PENs [11], and the MN is not encapsulated and does not have palisading nuclei whereas neurilemomas and PENs are encapsulated [21].

Neurofibromas are not encapsulated and have no palisading, but neurilemmal cells and possibly fibroblasts participate in their formation, resulting in irregular combinations of these elements [22]. However, plexiform neurofibromas (PN), atypical types of neurofibromas, may be confused with mucosal neuromas, because both tumors have similar microscopic findings [23]. Epithelial membrane antigen (EMA) is the most useful marker in differentiating MN from plexiform neurofibroma immunohistochemically. The perineurial cells of the former show the marker and tumor cells of the latter do not [23]. Although the immunohistochemistry of our case showed weakly positive of EMA, almost all plexiform neurofibromas occurred in patients with neurofibromatosis type 1 (NF1). Furthermore, the microscopic examination of the plexiform neurofibroma usually shows enlarged nerve bundles and the interstitium mostly mucoid, so the histological features of our case still resembled MN.

Some studies have shown that the proliferating nerve bundles express EMA, suggesting that the nerve bundles have differentiated to the perineurial cells [33]. While other studies have shown that there is no EMA-positive nerve bundle membrane, the author speculates that it may be due to the poor immunohistochemical technique or insufficient differentiation of the perineurial cells [9]. In our case, the structure of the nerve bundle membrane is obvious under the microscope, and EMA is positively expressed in the epithelial area, so we infer that the weakly positive reaction may be caused by insufficient differentiation of the perineurial cells.

MNs occur in the oral cavity, especially in the gingival papilla, which is also easy to be confused with other tumor-like lesions such as epulis [31]. As a most common type of epulis, peripheral ossifying fibromas often show pink-colored, tough, and well-defined mass the same as MNs. Peripheral ossifying fibromas can occur in all age groups but are more common in 10 to 40 years old. Histologically, peripheral ossifying fibromas usually show a stromal fibroblastic proliferation with intermixed hypermineralized bony tissue under HE staining, so we can differentiate MNs from peripheral ossifying fibromas.

MNs usually occur in the oral cavity as a component of MEN 2B, which is a syndrome of multiple MNs, medullary thyroid carcinoma (MTC), pheochromocytoma (PCC), bumpy lips, and marfanoid habitus, although not always concurrently. Oral MNs are the most common component among these components, presenting usually at early infancy, and are most often found in the lips, tongue and buccal mucosa, other less common sites being the palate and gingiva [4, 24]. When the lips are involved, the lips are diffusely enlarged (bumpy lips). When the tongue and buccal mucosa are affected, they appear as semicircular nodules or pimples.

Therefore, MEN 2B can be diagnosed by the special face caused by MN, the clinical manifestations of MTC, PCC and radiography, biochemical examinations, and it can be diagnosed early by detecting mutations in RET proto-oncogene. Other clinical signs of the patients with MEN 2B can also be considered in the diagnosis of oral lesions such as an MN [25]. Because MTC metastases can occur within 1 year of birth in MEN 2B patients, prophylactic thyroidectomy is recommended [26]; patients with PCC should also undergo tumor resection; plastic surgery may be considered when diffuse hyperplasia of a neuroma causes special features.

MEN 2B is an autosomal dominant genetic disease. After the diagnosis of MEN 2B, the patients' immediate family members should be screened for MTC and PCC, and early genetic testing for RET proto-oncogene mutations is necessary to achieve the purpose of early discovery and early treatment [27–29]. Our patient showed no abnormalities in the skeletal structure, lip shape, sonographic examination of the thyroid, or in any of the endocrine examinations, and there were no tumors elsewhere in the oral cavity or the ocular region.

MN without MEN 2B is very rare, a total of 19 cases have been reported including the case reported in this article. A solitary MN is present in the absence of other diagnostic signs, so it is necessary to combine the clinical examination, histopathological evaluation, IHC, radiography, and biochemical studies. Our patient was diagnosed as a solitary gingival mucosal neuroma without MEN 2B. Nevertheless, some investigators have suggested that MTC and PCC appear later [25, 30]. Thus, follow-up studies including radiography, endocrine examinations are necessary.

Conclusions

This study showed a rare mucosal neuroma in the gingiva papilla without MEN, the histopathological evaluation and immunoreaction of S-100 protein, EMA, NSE and NFP staining can be helpful in the differential diagnosis of MN. It is hoped that a greater understanding of MN without MEN in the oral cavity will avoid potential misdiagnosis, and contribute to determining the correct management, which appears to be complete surgical excision with close follow-up for recurrence and other components of MEN surveillance.

Abbreviations

MN: Mucosal neuroma; MEN: Multiple endocrine neoplasia; MEN 2B: Multiple endocrine neoplasia type 2B; MTC: Medullary thyroid carcinoma; PCC: pheochromocytomas; ONTs: Oral neural tumors; SCN: Solitary circumscribed neuromas; PEN: Palisaded encapsulated neuroma; PD: Probing depth; CAL: Clinical attachment loss; BOP: Bleeding on probing; EMA: Epithelial membrane antigen; NFP: Neurofilament protein; NSE: neuron specific enolase; PN: Plexiform neurofibromas; NF1: Neurofibromatosis type 1; HE: hematoxylin-eosin; IHC: Immunohistochemistry.

Declarations

Acknowledgements

We thank Dr. Jing-jing Sun in Department of Oral Pathology of Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine for a help to confirm the diagnosis.

Authors' contributions

CQ collected the patient's data, performed the surgery, made the review and drafted the manuscript. LZW prepared and observed pathology specimens and also drafted part of the manuscript. HWC, managed the patient and collected part of the data. ZCS helped to give the diagnosis and draft the manuscript. All authors have read and approved the final manuscript.

Funding

This study was supported by grants from the Clinical Research Program of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (JYLJ038), Shanghai, China.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1. Summary of MN without MEN 2B cases reported until 2019

Reference	Country	Patients(n)	Age(y)	Sex	Location	Clinical presentation	Treatment	Diagnosis approach	Recurrence	Follow-up
Attar B et al. (1986) [5]	USA	1	58	M	Rectosigmoid colon	Intermittent mid-left quadrant pain for 3 to 4 years, associated with constipation	Excisional biopsy	Histology, radiologic and biochemical studies	NA	NA
Miura H et al. (1989) [7]	Japan	1	68	M	Bronchia	Cough with sputum for 10 months, weight loss and the detection of severely atypical squamous metaplasia in a mass survey	Excisional biopsy	Histology, IHC (S100, positive), radiologic and biochemical studies	NA	NA
Higashide Y et al. (1997) [8]	Japan	1	14	F	Conjunctival fornix	NA	Excisional biopsy	Histology, IHC (S100 and EMA, positive) and generalized screening (no detail described)	NA	NA
Pujol RM et al. (1997) [13]	Spain	1	35	F	Tongue and lip	Multiple painless papules for 28 years	Excisional biopsy	Histology, radiologic, biochemical and molecular genetic studies	None	22 years
Gordon CM et al. (1998) [14]	UK	4	15, 12, 18, 4	2F, 2M	2 tongue, 1 corner of the mouth, 1 face (lip, eye, nose and buccal mucosa) *	NA	Excisional biopsy	Histology, radiologic, biochemical and molecular genetic studies	1	3-10 years
Gómez JM et al. (1998) [12]	Spain	2	15, 39	F	Tongue	NA	Excisional biopsy	Histology, radiologic, biochemical and molecular genetic studies	None	5 years
Shimazaki T et al. (2003) [9]	Japan	1	73	M	Larynx	Hoarseness and prickly sensation in the throat for 3 months	Excisional biopsy	Histology, IHC (S100 and NSE, positive), radiologic and biochemical studies	NA	NA
Jashnani KD et al. (2003) [17]	India	1	7	F	NA	NA	Excisional biopsy	Histology, radiologic and biochemical studies	1 (at 17-year-old)	>10 years
Nishihara	Japan	1	49	F	Hard palate	Painless	Excisional	Histology,	None	7

K et al. (2004) [16]						swelling on the hard palate for 4 years	biopsy	IHC (S100 and EMA, positive, NFP, negative), radiologic and biochemical studies		months
He PJ et al. (2005) [10]	China	1	65	F	Throat	Hoarseness and prickly sensation in the throat for 3 months	Excisional biopsy	Histology, IHC (S100, NFP and NSE, positive) and radiologic studies	None	1 year

Table 1. Summary of MN without MEN 2B cases reported until 2019 (Continued)

M, male; F, female; NA, not available; IHC, immunohistochemical; S100, S100 protein; EMA, epithelial membrane antigen; NFP, neurofilament protein; NSE, neuron specific enolase.

Reference	Country	Patients(n)	Age(y)	Sex	Location	Clinical presentation	Treatment	Diagnosis approach	Recurrence	Follow-up
Mao RJ et al. (2011) [15]	China	3	30, 42, 45	F	2 throat and 1 tongue	Hoarseness and prickly sensation in the throat	Excisional biopsy	Histology, IHC (S100, NFP and NSE, positive, EMA, negative) and radiologic studies	None	6~20 months
Erdem I et al. (2018) [6]	Turkey	1	67	F	Bronchia	Dyspnea, chest pain and fatigue	Excisional biopsy	Histology, radiologic and biochemical studies	NA	NA

* The patient who had facial neuromas recurred after each excision, extending along her left eye, nose, lips, and buccal mucosa.

Figures

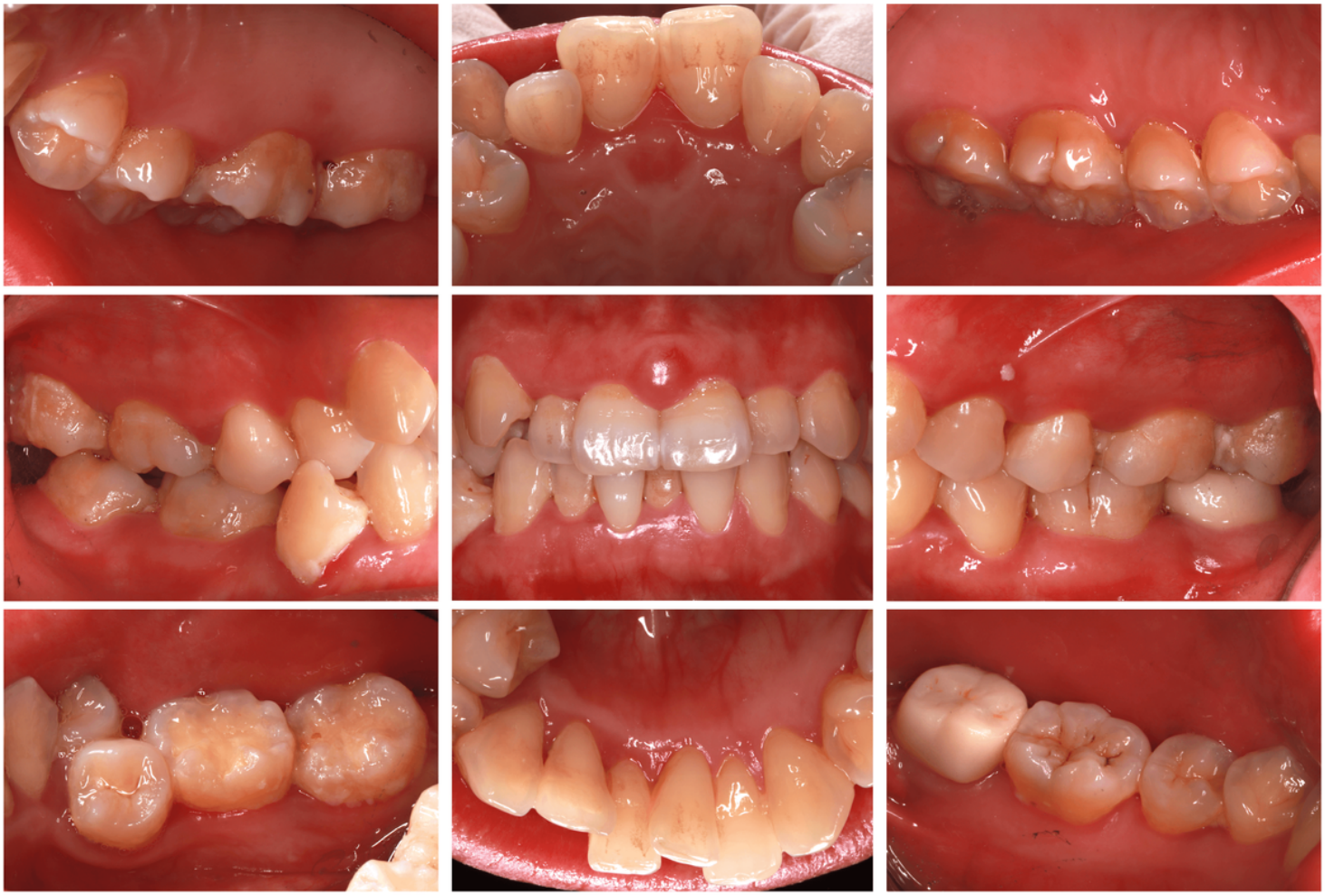

Figure 1

Intraoral photograph. At baseline, intraoral examination revealed a small, pink-colored, well-defined mass in the patient's labial gingival papilla between maxillary central incisor (teeth nos. 8 and 9).

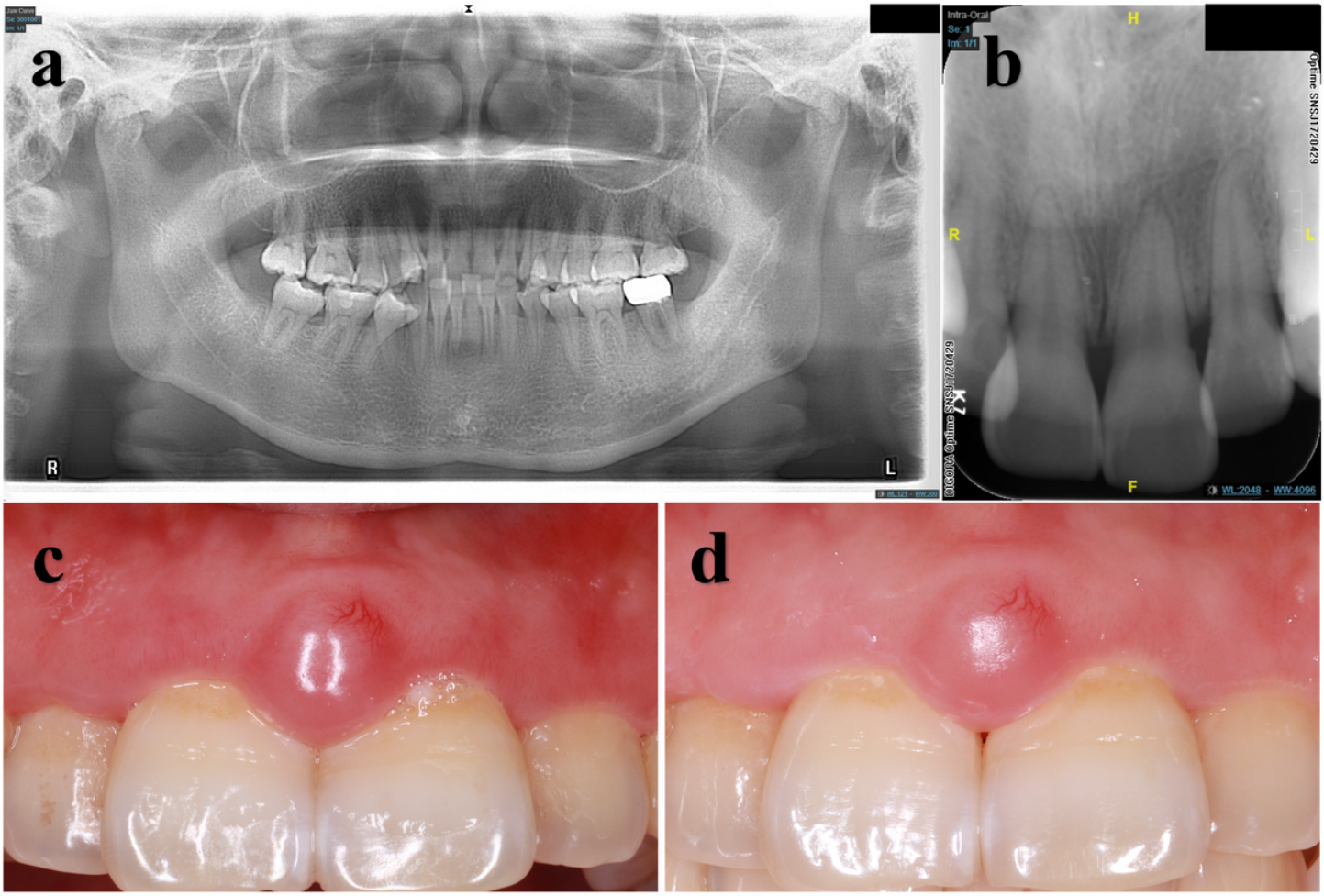

Figure 2

Radiographic examination and clinical photographs before and after periodontal initial therapy. Except for tooth no. 18, there were no obvious alveolar bone resorption and other abnormalities in the imaging performance of the remaining teeth. (a) Oral Panoramic Radiograph. (b) Digital periapical film. After periodontal initial therapy, there was no significant change in the size of the mass. (c) Base line. (d) After initial therapy.

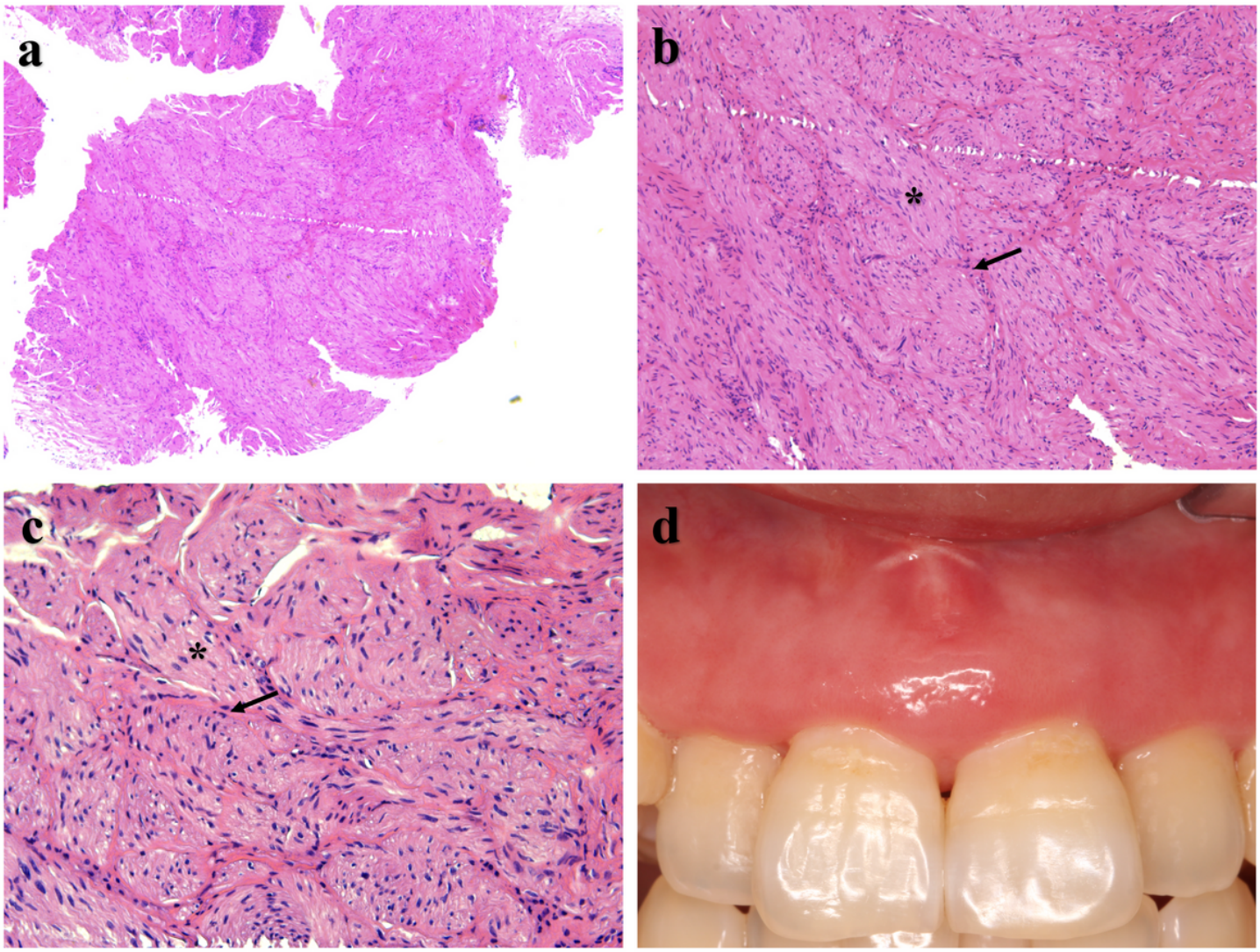

Figure 3

Histological hematoxylin and eosin photomicrographs. Histologically, irregular tortuous bundles of nerve cells (asterisks) with prominent perineurium (arrows) that lie scattered throughout the submucosa can be seen under HE staining (a to c). Magnification: ×50 (a), ×100 (b), ×200 (c). 3 months after operation, the operation area heals well (d).

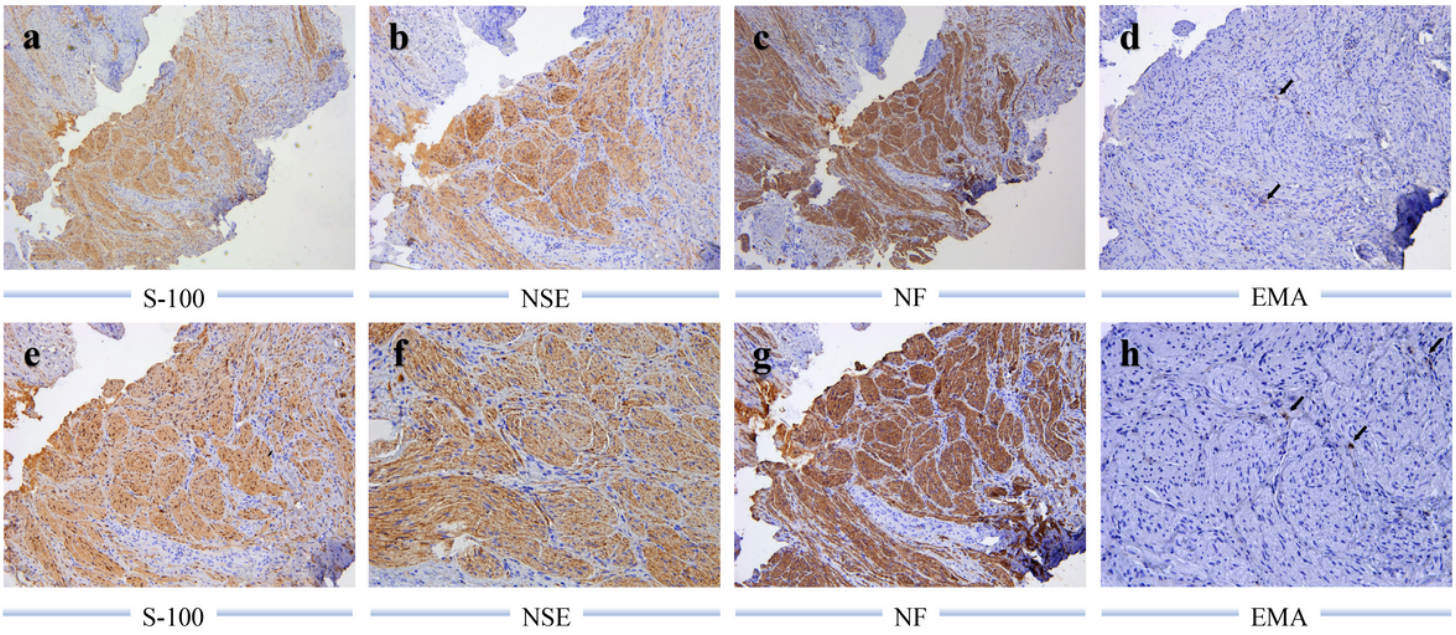

Figure 4

Images of immunohistochemical results of mucosal neuroma. Irregular tortuous bundles of nerve cells stain strongly positive of S-100 (a, e), NSE (b, f), NF (c, g) and perineurial cells stain weakly positive (arrows) of EMA (d, h). Magnification: ×50 (a, c), ×100 (b, d, e, g), ×200 (f, h).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- checklist.pdf