Peer Review File

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Reviewer A

Comment 1：

The authors provide a well-written case report of a gingival MN in a patient without MEN2B. However, the microscopical features available in figures 3 and 4 make the diagnosis of MN questionable since prominent perineurium positive for EMA, Glut-1 or Claudin-1 is absent. Indeed, there are some overlapping features with other conditions eventually associated with the nasopalatine nerve of otherwise healthy patients such as traumatic neuroma and neural hamartoma.

Replay 1:

Thank you very much for this positive feedback on the overall quality of our manuscript and this case! Histologically, mucosal neuromas consist of irregular, twisted proliferating nerve bundles encased by thick and distinct perineurium. In our case, the prominent perineurium could be seen microscopically after HE staining. Immunohistochemically, the positive expression of EMA was not prominent, but there are still some of the positively stained perineurial cells could be captured. Combined with the report of Shimazaki et al [1] we considered the weak positivity of EMA which could be caused by insufficient differentiation of perineurial cells.

In addition, we ruled out the diagnosis of traumatic neuroma because the patient explicitly denied a history of trauma. Moreover, neural hamartoma is often observed as enlarged and hyperplastic unmyelinated nerve fibers without perineurium, and hyperplastic fibers, fat and other connective tissues are seen between the nerve fibers histologically. Therefore, the diagnosis of neural hamartoma was ruled out by the histologic presentation.

[1] Shimazaki T, Yoshida Y, Izumaru S, Nakashima T. Laryngeal solitary multiple mucosal neuromas without multiple endocrine neoplasia (MEN) type 2B. Auris Nasus Larynx. 2003;30(2):191-195

Reviewer B

This case reports a patient with solitary mucosal neuroma of the gingiva. Most patients with MN are also accompanied by the characteristics of pheochromocytoma and medullary thyroid carcinoma, but this patient is a solitary MN which is a rare case. After surgery, the patient's prognosis is good. However, the author still needs to add some content in the discussion section to further increase the value of this article, especially the literature review mentioned in the Title.

Comment 2:

In the Discussion, the author focused on the difference between MN and other oral neurogenic tumors. In addition to this, the author should also add relevant features of MEN 2B, including clinical manifestations, endocrine examinations, and pathological features. What are the differences between these features and the occurrence of MN alone? It is recommended that the author present the table more clearly to diagnose the occurrence of solitary MN.

Replay 2:

Thank you very much for this comment. MEN 2B , or the mucosal neuroma syndrome, is an autosomal dominant genetic disease caused mainly by Met918Thr germline RET mutation, which is a syndrome of multiple MNs, medullary thyroid carcinoma (MTC), pheochromocytoma (PCC), bumpy lips, and marfanoid habitus, although not always concurrently[2].

MNs of MEN 2B may be present on the eyelids, conjunctiva, tongue, lip, intestinal tract, palate, pharyngeal and generally develops from early childhood with prominent "blubbery" lips, submucosal nodules on the vermilion border and MNs on the anterior dorsal surface of the tongue, etc[3]. Physical examinations may reveal an elongated face, lower jaw protrusion, large hands and feet and relatively long extremities[4]. HE staining of MN showed different sizes of nerve bundles surrounded by normal connective tissue under the microscope, and the nerve bundles were wrapped by a thick nerve bundle membrane. Immunohistochemical features were positive of S-100 protein for nerve bundle, and the surrounding nerve bundle membrane was immunoreactive for epithelial membrane antigen (EMA).

In addition, MTC commonly develops in all subtypes of MEN 2 and is the most important prognostic factor. Usually, MTC develops relatively young, exhibits a more aggressive disease course, and accounts for more than 95% of MEN 2B cases. MTC can be screened by thyroid function tests, thyroid ultrasonography and biochemical tests (e.g. serum calcitonin).

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, while solitary MN occur without the other abnormality about MEN 2B we mentioned above.

Moreover, We have organized the year of publications, authors, countries, clinical location of the cases, diagnosis methods, treatment methods, pathological features and prognosis of the relevant 8 cases into a table, as detailed in **Table 1**.

[2] Castinetti F, Waguespack SG, Machens A, Uchino S, Hasse-Lazar K, Sanso G, et al. Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study. Lancet Diabetes Endocrinol. 2019,7(3):213-220.
[3] Morrison PJ, Nevin NC. Multiple endocrine neoplasia type 2B (mucosal neuroma syndrome, Wagenmann-Froboese syndrome). J Med Genet. 1996,33(9):779-782.
[4] Lee MJ, Chung KH, Park JS, Chung H, Jang HC, Kim JW. Multiple Endocrine Neoplasia Type 2B: Early Diagnosis by Multiple Mucosal Neuroma and Its DNA Analysis. Ann Dermatol. 2010,22(4):452-5.

Changes in the text:

Page 6 Line214-223: "MNs of MEN 2B may be present on the eyelids … MTC can be screened by thyroid function tests, thyroid ultrasonography and biochemical tests (e.g. serum calcitonin)."
Page 6 Line224-230: "MEN 2B is an autosomal dominant genetic disease … 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."

Comment 3:

MN may occur in different organs. What are the characteristics of clinical manifestations when it occurs in these different organs? This also helps to clarify the diagnosis of MN. Since this is a very rare disease and the diagnosis is relatively complicated, a detailed discussion of the diagnosis will make this article more valuable.

Replay 3:

Thank you very much for this comment! MN may occur in rectosigmoid colon[5], bronchi[6, 7], conjunctiva[8], laryngeal[9-11], tongue[11-14], lip[12] and hard palate[15].

MN of the throat often causes hoarseness and prickly sensation in the throat, occasionally had a cough with sputa, but there is usually no pyrexia or dysphagia. Meanwhile, patients with MN of the bronchi often had a cough with sputa. MN present on intestinal tract often causes stomachache and constipation and MNs of the oral cavity are usually painless but may interfere with eating or cause oral and maxillofacial deformities. Moreover, MN of the conjunctiva MN in the conjunctiva can cause foreign body sensation and dry eyes.

In our case, the patient's solitary MN on the gingiva was painless, but the upper anterior gingival mass affected the aesthetic appearance.

[5]Attar B, Khurana D, Hlaing-Ray V, et al. Mucosal neuroma of the rectosigmoid colon. Gastrointest Endosc. 1986,32(3):219-220
[6]Erdem I, Duman D, Eroglu S, et al. Endobronchial Mucosal Neuroma with Sarcoidosis. J Coll Physicians Surg Pak. 2018,28(2):162-163
[7]Miura H, Kato H, Hayata Y, et al. Solitary bronchial mucosal neuroma. Chest. 1989,95(1):245-247
[8]Higashide Y, Nemoto Y, Imamura T. A case of conjunctival mucosal neuroma without multiple endocrine neoplasia. Nippon Ganka Gakkai Zasshi. 1997,101(7):621-625

[9]Shimazaki T, Yoshida Y, Izumaru S, Nakashima T. Laryngeal solitary multiple mucosal neuromas without multiple endocrine neoplasia (MEN) type 2B. Auris Nasus Larynx. 2003,30(2):191-195
[10]He PJ, Li XM, Zhou L, et al. Pharyngolaryngeal solitary multiple mucosal neuromas without multiple endocrine neoplasia type II b. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2005,40(4):311-312
[11]Mao RJ, Zhong YP, Peng GG, et al. Clinicopathological features of multiple mucosal neuroma without multiple endocrine neoplasia type IIB. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2011,46(8):681-683
[12]Gómez JM, Biarnés J, Volpini V, Martí T. Neuromas and prominent corneal nerves without MEN 2B. Ann Endocrinol (Paris). 1998,59(6):492-494
[13]Pujol RM, Matias-Guiu X, Miralles J, Colomer A, de Moragas JM. Multiple idiopathic mucosal neuromas: a minor form of multiple endocrine neoplasia type 2B or a new entity. J Am Acad Dermatol. 1997,37(2 Pt 2):349-352
[14] Gordon CM, Majzoub JA, Marsh DJ, et al. Four cases of mucosal neuroma syndrome: multiple endocrine neoplasm 2B or not 2B. J Clin Endocrinol Metab. 1998,83(1):17-20
[15] Nishihara K, Yoshida H, Onizawa K, et al. Solitary mucosal neuroma of the hard palate: a case report. Br J Oral Maxillofac Surg. 2004,42(5):457-459

Changes in the text:

Page 6 Line 234-240: “MN occurs in different organs with different clinical manifestations. MN of the throat often causes … MN of the conjunctiva MN in the conjunctiva can cause foreign body sensation and dry eyes (22).”

Comment 4：

Other case reports of MN in the oral cavity should also be the focus of this article. In particular, the author added literature review in the title, but the current article lacks discussion in this regard. It is recommended that the author organize the clinical features, pathological features, diagnosis methods, treatment methods and prognosis of the relevant 8 cases into a table, which can allow readers to more clearly and intuitively understand the characteristics of independent MN that occurs in the oral cavity.

Replay 4:

Thank you very much for this comment. We have organized the year of publications, authors, countries, clinical location of the cases, diagnosis methods, treatment methods, pathological features and prognosis of the relevant 8 cases into a table, as detailed in **Table 1**.

Changes in the text:

Table 1

Other concerns:

Comment 5：

“Case report” in the Keywords is suggested.

Replay 5:

Thank you very much for your reminder. We have now added "Case report" in the Keywords.

Changes in the text:

Page 2 Line 58: We have added "Case report" in the Keywords.

Comment 6:

Because mucosal neuroma is an autosomal dominant genetic disease, the author should write down the patient's family history and whether genetic testing has been performed in Case presentation.

Replay 6:

Thank you very much for this comment! The patient had denied family history but was not considered for genetic testing at this time. In our report, the 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.

Changes in the text:

Page 3 Line 91-92: She denied family history but did not undergo genetic testing.

Comment 7:

A timeline figure is suggested.

Replay 7:

Thank you very much for this comment! We have added a timeline figure for our case.

Changes in the text:

Page 4 Line 139-140: The Timeline of diagnosis, treatment and follow-up of this case are shown in Fig. 5.

Page 11 Line 421-422: Fig. 5 Timeline of diagnosis, treatment and follow-up. The patient is still being followed up every 6 months.

Comment 8:

What are the strengths and limitations of this case series? Is there something better that can be done in the diagnosis and treatment? Please provide this content.

Replay 8:

Thank you very much for this comment! The strength of this case is that it is the first report of a solitary MN without MEN 2B occurs in the gingival papilla and a full literature review and summary. The limitation is that due to the high cost of testing and COVID-19 pandemic, the patient had declined genetic testing and we can only diagnose solitary MN by clinical examination pathological features and ancillary laboratory tests.

Comment 9:

The primary take-away lessons should be reconsidered after add more discussion mentioned above.

Replay 9:

Thank you very much for this comment! We have added discussion mentioned above in the text. In conclusion, although the patient had refused to undergo genetic testing, this case can still be

diagnosed as a solitary MN based on the clinical examination, pathological features and ancillary laboratory tests.