

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name " 70289-maintext file"). We hope that the revised version will fulfill the requirements for publication in the World Journal of Clinical Cases.

Name of journal: World Journal of Clinical Cases

Manuscript NO: 70289

Manuscript type: Case report

Title: Hemangioma in the lower labial vestibule of an eleven-year-old girl: A case report

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Reply to editorial comments:

Reviewer #2:

I suggest a further discussion of the pathogenesis of intraoral hemangioma, if there are relevant research advances.

As mentioned in the manuscript, "Capillary hemangioma is a common lesion, but it rarely occurs in the oral cavity. According to Matsumoto et al., 45.2% of capillary hemangiomas occurred on buccal mucosa, 35.5% on the tongue, and only a small percentage occurred in the lip, gingiva and palate[4]." Therefore, a summary of the literature on intraoral hemangioma would further enhance dentists' understanding of the disease.

In 1982, vascular anomalies were categorised into two main categories: vascular malformations and vascular tumors. Hemangiomas are true neoplasms represented by increased rate and proliferation of endothelial cell turnover. On the other hand, vascular malformations are localised abnormality and disorganisation of the blood vessel caused by defects in vascular development. ^[1-3]. Simple vascular malformations are classified histologically, based on the vessel size, into capillary, venous, lymphatics, arteriovenous fistula, and arteriovenous malformations.

Vascular lesions are further categorised into non-harmful, locally destructive, and malignant lesions^[4]. Namely, hemangioma is a neoplasm of endothelial origin which is commonly found in the early years of life and then the neoplasm regresses gradually with age^[5]. Intraoral and intramuscular hemangiomas are rare, dissimilar to cutaneous and subcutaneous hemangiomas. Oral hemangiomas could occur in more than 6% of infants and have high prevalence in female presenting 3:1 (female: male). Infants are more likely to develop oral hemangiomas if they fall in one of the following conditions; infants who are born to older mothers, twins or triplets, premature, or have low birth weight^[6]. Hemangioma is a common vascular benign tumor which falls under the category of benign vascular tumors and it is further divided into capillary and cavernous hemangioma^[2].

Capillary hemangioma is a common lesion, but it rarely occurs in the oral cavity. According to Matsumoto et al., 45.2% of capillary hemangiomas occur on buccal mucosa, 35.5% on the tongue, and only a small percentage occur in the lip, gingiva and palate^[7]. Capillary hemangiomas are firm in consistency and have a limited history of symptoms.

Science editor:

This disease is rare, but the author's discussion is not enough. To discuss the mechanism of hemangioma, and to summarize the clinical manifestations, diagnosis, and treatment of hemangioma in different sites.

Although the exact cause of oral hemangioma is not fully understood, hormonal changes, embolic phenomenon and genetic mutations are believed to play an important role in the tumor development^[8].

Hemangiomas are hypothesised to develop because of both angiogenesis and vasculogenesis through three different stages, as follows: endothelial cell proliferation stage, rapid growth stage and spontaneous disappearance. Endothelial cell proliferation is stimulated by many factors, such as basic fibroblast growth factor, vascular endothelial growth factor and transforming growth factor-beta. Then, the quantity of endothelial cells is sustained, and each cell increases in size, leading to comprehensive enlargement of the structure size. At the end, spontaneous involution occurs when the endothelial cells are replaced by connective tissue, adipose, and fibroblast, and the number of small vessels decrease in quantity^[9].

Hemangioma could be classified clinically as congenital or infantile (previously named strawberry or juvenile). Congenital hemangioma presents at birth and does not demonstrate proliferation stage. In contrast, infantile hemangioma may develop at the first months of the infant life and show a proliferative phase during the period of six to twelve months; then, most cases spontaneously regress between the age of six to nine years. High percentage of hemangiomas disappear completely in childhood, with < 20% carrying on to puberty^[10, 11]. Oral hemangioma presents as a solitary, soft, fluctuant, compressible, smooth, red, or bluish submucosal mass. Significant variations may present based on the depth and site of the mass. Superficial masses are easy to visualise and may present as pedunculated, sessile, or

lobulated and reddish in colour. In contrast to deeper masses, they appear as a dark blue discolouration recognisable from surrounding normal colour mucosa. It also reveals tenderness on palpation and blanch on compression with glass slide (positivediascopy test)^[12]. In this case, the differential diagnosis of the tumor was written down as vascular anomalies, including hemangioma, and vascular malformation, including venous, capillary, lymphatic and arterial malformations. Salivary gland tumor, mucocele and angioleiomyoma were also considered.

It is worth mentioning that vascular malformations, salivary gland tumor, mucocele and angioleiomyoma were all excluded because the lesion showed a slow-flow vascular lesion by using Colour-Doppler-ultrasound, which is highly consistent with hemangioma.

Hemangioma is mostly characterised by its benign feature and has high tendency of involution by itself over time. However, sometimes hemangioma requires intervention, especially in case of impairment in breathing, swallowing and speech. The first line of evaluation and diagnosis would be by Color-Doppler ultrasound imaging. This imaging modality is non-invasive, cost-effective and has no risk of radiation. If intraosseous lesion is anticipated, other imaging modalities could be useful for the diagnosis, such as a contrast-enhanced magnetic resonance imaging (MRI), computed tomography (CT), and angiography^[13]. A contrast-enhanced MRI and CT imaging identify the shape, size, and calcification of the tumor. The Color-Doppler ultrasound imaging modality was the suitable choice for the patient due to many factors, such as financial issues and the age of the patient^[14].

Choosing a suitable method for managing hemangioma is based on multiple factors such as the aesthetic consideration, clinical nature, size, site, growth rate, accessibility, extent of the tumor, and age of the patient. Hemangioma could be managed by different ways; for instance, surgical excision of the tumor, embolization, electrosurgery, cryosurgery, laser, steroid injection, or sclerosing materials. In case of small oral hemangioma, the commonly used method is the total surgical excision of the whole mass to decrease the potential risk of recurrence^[15]. However, if the lesion is large and located in a significant part of the mouth, such as the tongue, in this case the surgical excision of the lesion would not be preferred, so as to avoid post-surgical complications in swallowing and speech. Sclerotherapy is recommended to manage large hemangiomas in the oral cavity in which 3% sodium tetradecyl sulfate or ethanolamine oleate is injected into the main vessels of the lesion to destroy the endothelial cells, leading to lesion destruction.

The picture quality of figure 1b and Figure 2 needs to be improved.

The quality of the pictures was improved by using Photoscape

The references are too few and should be supplemented.

The following references were added:

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This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

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Please find the uploaded (pdf) for more information regarding the fast-track Research funding program at Princess Nourah Bint Abdulrahman University.

Therefore, no grant number is available at this time. However, the corresponding author, Dr. Ashwag Aloyouny, will pay the publication charges.

Thank you for considering the review

Sincerely,

Ashwag Aloyouny