New treatment strategy for granulomatous epulis: Intralesional injection of propranolol

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Abstract

Epulis is a relapsing lesion in gingiva without specific treatment for its unexplained pathogenesis. Nowadays, surgical excision is the most popular method of treatment. To prevent recurrence, it is necessary to resect diseased tissues thoroughly, and even to remove the involved teeth. However, this may cause functional and cosmetic deformities. Therefore, it is urgent to find a new therapy without severe side effects. Infantile hemangioma is a common benign pediatric tumor which shares many features with epulis, such as rich vascularity, high incidence of female patients, high hormone level and similar treatments. A recent study showed that propranolol, a beta adrenergic receptor (β-AR) antagonist, was effective as treatment for infantile hemangioma. Our preliminary work showed that mRNA and protein levels of β2-AR were higher in epulis than in adjacent tissue. Therefore, we hypothesize that intralesional injection of propranolol may be useful as epulis treatment. Further work need to be done to confirm the safety and therapeutic effect of the treatment. After that, this specific β2-AR antagonist may be the first choice for epulis treatment.

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Epulis

Epulis is an inflammatory or tumor-like lesion in periodontal ligament and connective tissue of the alveolar process. It occurs at any gender and age, but is most prevalent in young and in females. Zheng summarized various classifications of epulis in the literature and concluded three main types: fibrous epulis, granulomatous epulis and giant cell epulis [1]. Type of injury or inflammatory process, oral hygiene, nutrition, alcohol, nicotine, pharmacotherapy, hormonal status, and immune efficiency may influence the initiation, development and involution of epulis [2]. In particular, angiogenesis, vasodilatation and increased capillary permeability regulated by estrogen were considered to be responsible for the development of the granulomatous epulis [3].

Simple surgical excision of involved gingiva has a high risk of recurrence despite sophisticated skills. Surgery with a wide margin (resection of a large portion of healthy tissue around the tumor, possibly including some bone) is the first treatment option for the disease. The teeth next to the epulis usually need to be removed as well. This method is often unacceptable for young patients because of functional defects and missing teeth. To avoid these side effects, some novel treatments have been presented in recent years. One therapeutic option is a combination of fibrous tissue excision with CO2 laser [4], controlling dental plaque, and prosthetic rehabilitation. Another is intralesional pingyangmycin injection. Wang et al. demonstrated that pingyangmycin treatment on 58 epulis cases markedly improved clinical appearance and satisfaction of patients [5]. However, these methods are not based on the pathogenesis of epulis, which is a big obstacle for an optimal treatment. With a distinct increase in public awareness of oral health in China, more and more epulis patients come to the hospital. It is extremely important to find a safe and effective treatment to satisfy their needs.

Infantile hemangioma

Infantile hemangioma (IH) is a common childhood tumor composed of disorganized blood vessels and immature hemangiomatic endothelial cells [6,7]. It is more common in females than in males at ratios of 3:1 to 5:1 [8]. A typical life cycle starts with the proliferation phase, which lasts for 3–9 months and is followed by a slow involution phase that will continue for 1–10 years. Most IHs will undergo spontaneous involution, but the rest may cause functional and cosmetic deformity in the specific region [9]. The estrogen level in IH, especially in the proliferation phase, is markedly higher than that in normal tissue [10]. Theories about the mechanism of IH mainly include placental origin, intrinsic defects, somatic
endothelial mutations, extrinsic factors creating a conducive environment for growth, and hemangioma stem cell differentiation [11,12], but those could hardly explain all the characteristics of IH.

Current medical and surgical interventions have been described thoroughly in the literature and include steroids, pingyangmycin injection, laser and surgical excision. However, there is a high risk of severe complications, and better choices are urgently needed [13]. In 2008, Léauté-Labrèze et al. reported their successful use of propranolol in 2 cases of IH associated with cardiac disease [14]. Since then, propranolol has become the first-line drug for treating IH worldwide. The effect of propranolol on IH was found incidentally, and the exact mechanism was unclear. However, many researchers believe that this might reveal the mechanism of IH. Propranolol is a representative beta adrenergic receptor (β-AR) antagonist that is non-selective with respect to β1- and β2-AR antagonism and has little impact on blocking β3-AR. Storch et al. considered that propranolol might interfere with endothelial cells, vascular tone, angiogenesis and apoptosis via β-AR in IH [15]. Recently, another β-AR antagonist, timolol, was reported to successfully treat IH on the eyelid [16]. In patients treated with the two β-AR antagonists, there was a close relationship between β-AR inhibition and IH involution.

**Hypotheses**

The outpatient numbers of epulis is very large in our Qilu hospital, especially that of granulomatous epulis, which accounts for about 57.2% of epulis, and is most common during pregnancy [17]. New treatments are needed as current surgery or laser-ablation therapies do not satisfy patient needs. It is appropriate to study the pathogenesis and then develop the specific medicine. Some clinical and histopathological characteristics of granulomatous epulis are similar to IH: granulomatous epulis is rich in vessels surrounded by edematous fibrous tissue, and easily bleeds when stimulated; the majority of patients are females; pregnancy epulis is usually accompanied by increased estrogen level and shows spontaneous regress after childbirth; the treatments, such as surgical excision, laser and intralesional injection of pingyangmycin, are also effective for IH [18]. In accordance with the key role of β-AR in hemangioma, these similarities imply that a β-AR-organized signaling module may be essential for the pathogenesis of epulis. Therefore, the use of β-AR in epulis may help us solve this problem.

Neither fibrous epulis nor giant cell epulis was common in clinic. Furthermore, the characteristics of hemangioma, such as rich vessels, high hormonal status and spontaneous regress, were also the characteristics of pregnancy epulis (a special type of granulomatous epulis). Therefore, we focused our hypothesis on granulomatous epulis. Under a human-subject protocol approved by the Committee on Clinical Investigation at Qilu Hospital, we obtained surgical specimens from 13 pregnant women with granulomatous epulis, which shows bright red surface, easy to bleed as being stimulated and recurrence. The clinical diagnosis was finally confirmed in the hospital’s pathology department by histological evaluation as rich in vessels surrounded by edematous fibrous tissue. Written informed consent was obtained for translational research about β-AR on tissue samples. All data were analyzed by SPSS 16.0. The Student’s t-test was used to evaluate the difference of β-AR expression. Differences were considered statistically significant for p value less than 0.05.

Our preliminary work proved that only the levels of β2-AR protein and mRNA were higher in epulis than in adjacent tissue, while there was no difference of β1- and β3-AR levels between the two tissues. Then, we obtained samples from 12 more patients with granulomatous epulis to detect the expression of β-AR, and the result was the same as before (Figs. 1 and 2). In the involution of epulis, propranolol may play a key role via β2-AR, which has the potential to induce gingival cells apoptosis, trigger vasoconstriction and block pro-angiogenic signals. β1- and β3-AR are likely to play only minor roles in this process. So far, no specific β2-AR antagonist has been used in clinic. Hence, we have a high unmet need for selective β2-AR inhibiting agents.

In clinic, oral administration of propranolol is used for severe IHs, who have extensive lesion of the whole body or are associated with other diseases. However, oral propranolol has system-wide effects, and may cause adverse effects such as bradycardia, diarrhea and changed sleeping pattern [19]. Intrallesional injection of propranolol improves the quantity and speed of regional β-AR inhibited and may reduce the system-wide side effects. Therefore, it may be a better choice for this localized disease, especially for pregnancy epulis, which is a type of epulis occurring in pregnant woman and spontaneously regressing after childbirth.

Based on the similarities of epulis and IH, effects of propranolol treating IH and our experimental results, we hypothesize that intrallesional injection of propranolol may be a safe and effective way
for elimination of epulis. Compared to other therapeutic strategies, this method has fewer side effects, less economic burden and better pertinency. Further studies should focus on security and effectiveness. Furthermore, the study on roles of specific β-AR subtypes, especially on β2-AR, is also intriguing.

Conflict of interest statement

None declared.

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