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Case Report

Local Bevacizumab Treatment of Juvenile-Onset Respiratory Papillomatosis Might Induce Multiple Tracheal Pyogenic Granulomas

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Key Words: Recurrent respiratory papillomatosis, bevacizumab, laryngeal application, adverse effect, pyogenic granuloma.

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INTRODUCTION

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is the most common pediatric neoplastic disease of the airway. Its estimated annual incidence is 0.17–1.34 per 100,000 children. Although multiple treatment strategies for JORRP exist, surgical debulking remains the therapeutic mainstay. In the last 10 years, the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, has been administered to adults and children with severe disease, and it has shown promising effects. For aggressive laryngeal disease, bevacizumab is administered with an intra-lesion or sub-lesion injection. When tracheobronchial involvement is extensive, intravenous bevacizumab administration might be considered.[1,2]

To date, no adverse effect has been reported for local bevacizumab applications. Here, we present the first case of a multiple tracheal pyogenic granuloma that developed after intra-epithelial bevacizumab application in a 2-year-old child.

Case Report

A 2-year-old girl had been diagnosed with JORRP at 1.5 years old. In the first year after the JORRP diagnosis, she underwent five microlaryngoscopies to ablate papillomas with a CO_2 laser. Each surgery was indicated by rapid papilloma recurrence and substantial worsening of voice quality, until aphonia occurred (Fig. 1). Each surgery included a tracheoscopy, and no spread of papillomas was detected in the trachea. Bevacizumab (25 mg/mL) was applied locally in the epithelial layer of the vocal cords during the third, fourth, and fifth surgeries, at doses of 12 mg, 16 mg, and 16 mg, respectively. Half the bevacizumab dose was applied under the lesion before papilloma ablation, and half was injected into the epithelium after papilloma removal. For the first four microlaryngoscopies, the airway was managed with endotracheal intubation. However, during the fifth surgery, supraglottic jet ventilation was applied when removing papillomas from the posterior section of the vocal cords and when injecting bevacizumab into the epithelium at the end of surgery.

During the sixth surgery, 3 months later, in addition to a significant papilloma recurrence in the vocal cords, a tracheoscopy revealed multiple white granular mucosal lesions that filled the trachea (Figs. 2 and 3). Nodules did not look like papillomas in white light. Moreover, imaging with the Karl Storz Image1 S system (KARL STORZ, Tuttlingen, Germany) showed no vascularization typical of papillomas (Fig. 4). A histopathological examination revealed granulated tissue with a fibrous "cap" on the surface, consistent with a pyogenic granuloma diagnosis. Based on this diagnosis, the physician chose to manage the child with careful observation over the following weeks. The post-surgical clinical course was uneventful. The child exhibited no dyspnea or significant cough. The next microlaryngoscopy, scheduled 4 months later, showed no evidence of a tracheal granuloma. During the most recent microlaryngoscopy, 4 months later, no tracheal granuloma was detected.

DISCUSSION

Bevacizumab is a human monoclonal antibody that binds to VEGF and prevents its interaction with VEGF receptors (VEGFRs). VEGF plays a role in JORRP development. Previous in vitro studies have shown strong

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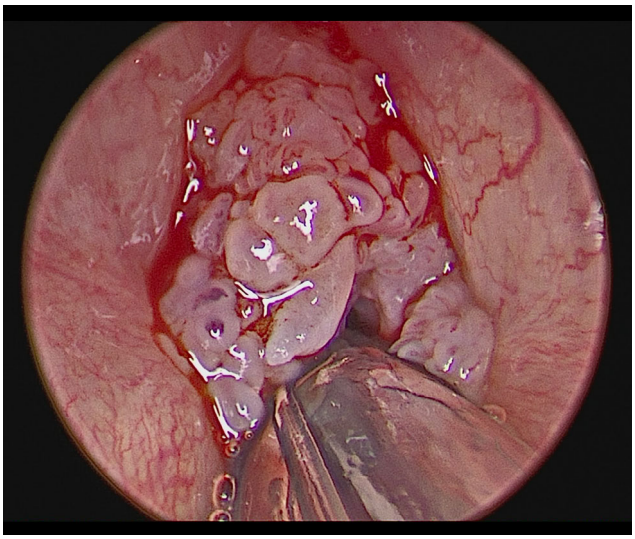

Fig. 1. Direct videolaryngoscopy. Both vocal cords are completely covered with papillomas.

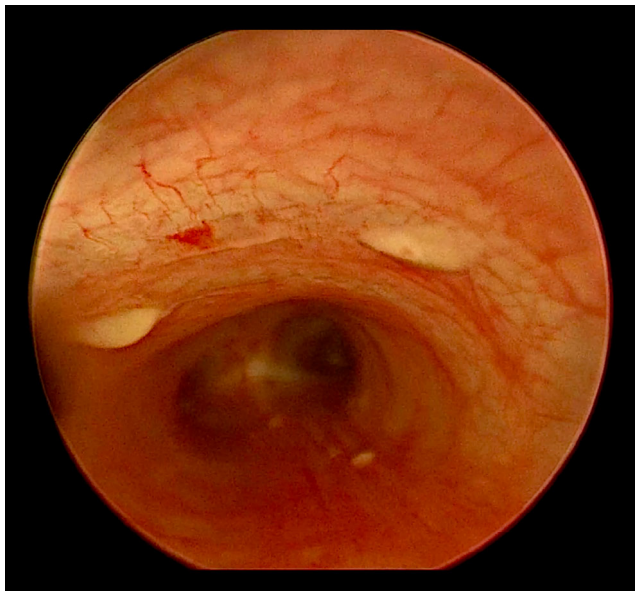

Fig. 3. Tracheoscopic image of the distal trachea shows multiple white granular mucosal lesions diagnosed as pyogenic granulomas.

expression of VEGF-A in papilloma epithelium and VEGFR-1 and VEGFR-2 messenger RNAs were detected in the underlying vascular endothelial cells.[1,2] Local intra-lesional and sub-lesional laryngeal bevacizumab injections have been used to treat JORRP with promising results more than 10 years. To date, no adverse effects of this treatment have been reported. Moreover, no detrimental vocal fold changes were observed during a study that investigated potential pathologic changes in porcine laryngeal specimens injected with bevacizumab.[1,2] However, paronychia, associated with a pyogenic granuloma, has been frequently mentioned among the specific side effects of VEGF inhibitors administered intravenously.[3]

Pyogenic granuloma is a polypoid, granulated tissue-like capillary hemangioma, with a controversial pathogenesis. It is hypothesized to be a nonspecific tissue reaction to various types of insults. It occurs on the skin and at mucosal surfaces. It might cause a pertinacious cough, and it could potentially obstruct breathing, when localized in trachea. Moreover, pyogenic granuloma was also

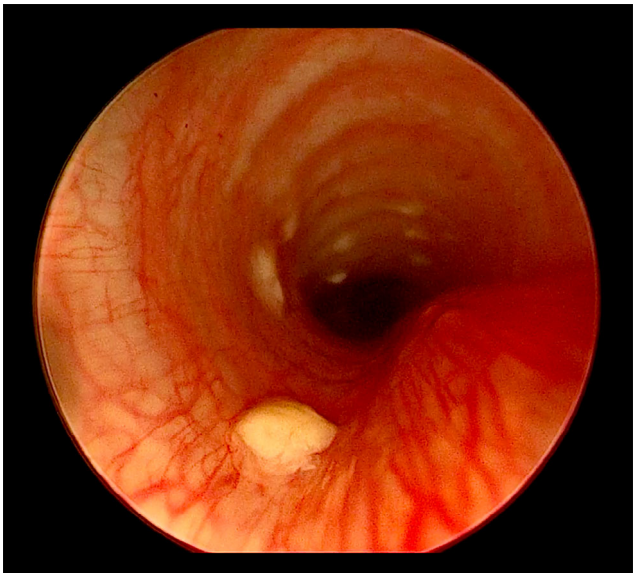

Fig. 2. Tracheoscopic image of the proximal trachea shows multiple white granular mucosal lesions diagnosed as pyogenic granulomas.

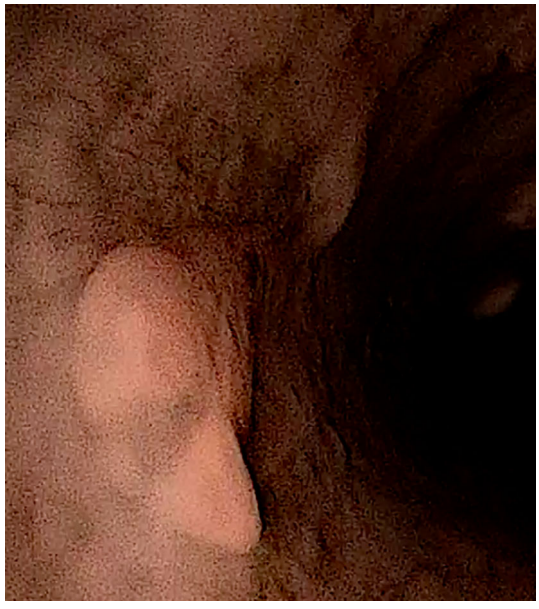

Fig. 4. Tracheoscopic image displayed in the KARL STORZ IMAGE 1S system. The vascularization typical of papillomas is not present on the granulomas.

reported to cause hemoptysis.[4,5] As of 2016, only 16 cases of solitary pyogenic granuloma of the trachea had been reported.[5] In addition, only one case of multiple pyogenic granulomas, remarkably similar to our case, was reported previously.[4] However, in that case, the granulomas developed in an adult patient after treating lung cancer intravenously with the epidermal growth factor receptor inhibitor, erlotinib.[4]

To our knowledge, this study was the first to describe multiple pyogenic granulomas in a child's trachea. We speculated that the pyogenic granulomas we observed developed due to a reaction in the tracheal mucosa against bevacizumab. It is highly likely that some bevacizumab had unintentionally penetrated into the trachea during an intra-epithelial laryngeal injection. Moreover, we speculated that the jet ventilation might have facilitated the spreading of bevacizumab into the trachea and tracheal epithelium. Due to the lack of another explanation for the presence of a pyogenic granuloma in the trachea of our patient, we made the diagnosis after ruling out other potential causes and based on similarities to a previously published case report of an adult patient.[4]

Several observations supported our diagnosis. First, although granulations might develop in the trachea in response to a wide range of mechanical airway irritations (eg, an intubation cannula or tracheostomy tube), those granulations looked different from the granulations we found, and they were typically localized in the areas where the cannula contacted the trachea. Moreover, no previous report mentioned that multiple pyogenic granulomas might occur as a side effect of jet ventilation. In addition, multiple pyogenic granulomas did not develop in our patient when endotracheal intubation was applied during a bevacizumab application in previous surgeries.

CONCLUSION

Due to the promising results observed in patients with JORRP, the number of patients that undergo laryngeal intra-epithelial bevacizumab injections is likely to grow. Therefore, it is important to alert clinicians about the potential side effects of administering bevacizumab locally. The present case report showed that bevacizumab could spread into the tracheal mucosa during jet ventilation and could induce multiple pyogenic granulomas. Therefore, we recommend avoiding jet ventilation during an intra-laryngeal bevacizumab injection.

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