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Intralesional use of Bevacizumab in Adult Recurrent Laryngeal Papillomatosis

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1. Introduction

Recurrent laryngeal papillomatosis (RLP) is a disease characterized by the development of exophytic proliferative lesions of the connective tissue, covered by epithelium, which affects the mucosa of the airways. The responsible agent is human papillomavirus (HPV) infection, and it has a great predilection for the larynx [1]. The most frequently found viral subtypes are HPV 6 and 11, in 90% of cases. Subtypes 16 and 18 are rarer in children with PLR, but if they are present there is a greater potential for malignancy [2].

Recurrent laryngeal papillomatosis has an incidence in the US of 4.3 per 100,000 in the pediatric population and 1.8 per 100,000 in adults [1]. In Peru, few studies have determined the epidemiology of papillomavirus, and there are no reports on the incidence of PLR. A study with 5,435 patients in the department of San Martín determined an incidence of HPV of 12.6% [3]. The presence of high-risk HPV was 33.6% in a study of 2,208 women in different cities of the country, and 34.49% in a study of 2,247 [4]. In an investigation with 1,099 individuals from a poor district of Lima, the presence of oral HPV and high-risk oral HPV was identified, 6.8% and 2.0%, respectively [5].

The virus initially infects the basal layer of the epithelium through minor abrasions. The E6 and E 7 proteins, expressed by the virus, inactivate the regulatory factor interferon, allowing the HPV infection to remain persistent and asymptomatic [6]. Additionally, an important factor in determining the reappearance of lesions is vascularity in tumor growth, initiated by vascular endothelial growth factor (VEGF) [7].

There is currently no consensus on the best and most effective single or combined treatment for the management of PLR. The most used method is surgery (CO2 laser, KTP, cold technique, microdebrider or tracheostomy), which maintains the objective of providing a safe airway avoiding complications of stenosis and voice disorders. However, the aggressiveness and recurrence of the disease makes the use of adjuvant therapy necessary in some patients [1, 2, 7].

The present case shows us a female patient diagnosed with recurrent laryngeal papillomatosis treated with the cold technique and bevacizumab as adjuvant therapy.

2. Clinical Case

A 53-year-old female patient, hypertensive controlled with valsartan and atenolol, without harmful habits. She presented a diagnosis of recurrent laryngeal papillomatosis since 1973, with 45 laryngeal microsurgeries (cold technique), the last of which was in September 2013. She presented with 42 years of disease characterized by persistent dysphonia and recent respiratory distress. The voice disability index-10 (VHI-10) was 28 at her admission. Flexible laryngoscopy revealed papilloma-cough lesions in the epiglottis, arytenoids, bands, aryepiglottic fold, and incomplete glottic closure (Figure 1).

The first surgery required a prior tracheostomy due to extensive airway compromise, and the tracheostomy was removed 5 days postoperatively. The resection of the papillomatous lesions was by means of video-assisted laryngeal microsurgery with a rigid endoscope and cold technique, and sublesional injection of 2 mL of bevacizumab at a concentration of 16.5 mg/mL (33 mg in total per dose, distributed in all the lesions). present). Two more infiltrations were performed, with an interval of 6 weeks, after nasofibroscopic evaluation. The control 12 months after the first application of bevacizumab showed an VHI-10 of 5, and absence of lesions (figure 2).

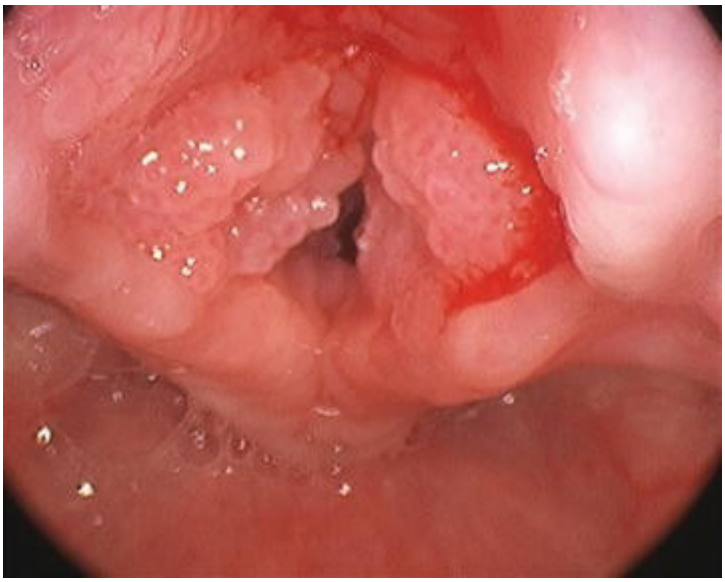

Figure 1: Papillomatosis in the larynx

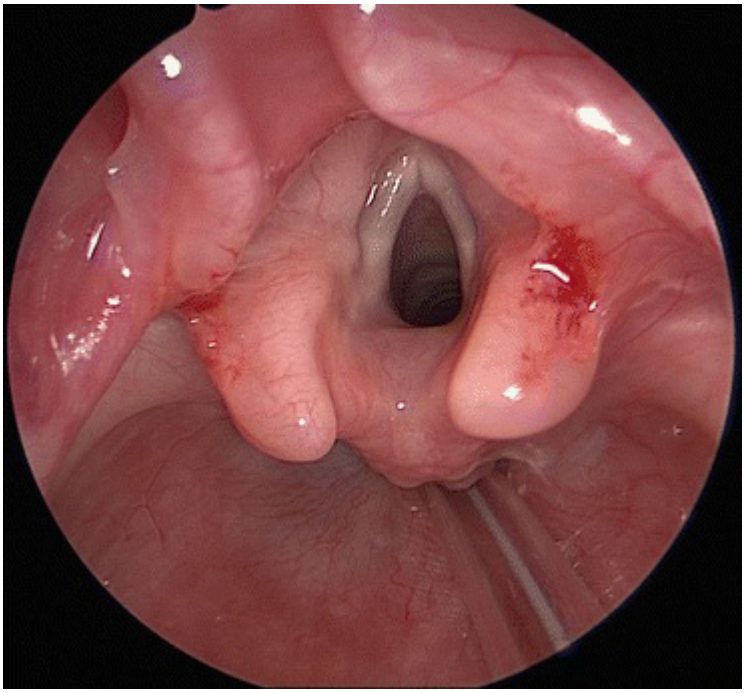

Figure 2: After 12 months of the first application of bevacizumab

3. Discussion

In the treatment of recurrent laryngeal papillomatosis, cidofovir is perhaps the most widely used adjuvant therapy. It has antiviral capacity against DNA viruses, and is believed to induce apoptosis and increase the immune response. However, there is no clear protocol regarding doses and frequencies, and a certain relationship with laryngeal dysplasia has been seen [2, 8]. Other less clear treatments are interferon, indole3-carbinol, cisretinoic acid, mumps vaccine, photodynamic therapy and HspE7 [1, 2].

In relation to future treatments, there are two that have aroused the most interest. The first is the human papillomavirus vaccine, reporting isolated clinical cases of the use of the vaccine as a treatment in patients with PLR. However, clinical trials are required in this regard to validate these data. Currently, there is a phase III study in children in Hungary, and another study in adults in the Czech Republic [1].

Bevacizumab represents another alternative in the therapeutic arsenal. This is a recombinant monoclonal IgG1 antibody that binds extracellularly to vascular dothelial growth factor (VEGF), preventing its interaction with VEGF receptors on the surface of endothelial cells, and inhibiting angiogenic activity. It has been used for different neoplàsia.

The first pilot with sublesional bevacizumab and KTP laser evaluated 10 adult patients in 2009, and concluded with a reduction of more than 90% in recurrence, and with 4 patients with total resolution [9]. Subsequently, a prospective study with 20 patients,

4 injections at an interval of 6 weeks, showed a 95% reduction in lesions at 4 months [10]. Regarding the safety of the drug and dose, it has been determined that a concentration of up to 25 mg/mL of bevacizumab is safe in pediatric patients, even in patients with severe PLR who require more than 4 surgeries per year [12, 15]. Another study in 43 patients, with 100 laryngeal injections of bevacizumab, showed that a dose of 15 to 50 mg is safe, without any systemic or local complications [11].

In our hospital we do not have a KTP laser, so laryngeal microsurgery with cold excision was performed. Subsequently, the sublesional injection of bevacizumab was carried out, repeated twice. It is important to highlight the great improvement in voice, and the absence of lesions at 12 months of follow-up.

In conclusion, the use of sublesional bevacizumab represents a safe alternative for the adjuvant treatment of recurrent laryngeal papillomatosis, both in adults and children.

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