

## CASE REPORT

# Recurrent Laryngeal Papillomatosis: A Laser CO<sub>2</sub> Surgery and Bevacizumab Intralesional Injection as Adjuvant Therapy

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## ABSTRACT

We present a case of recurrent respiratory papillomatosis (RRP) transformed in a lobular intraepithelial neoplasia LIN 2 vocal fold lesion treated with a microdirect laryngoscope with 10,600-nm laser CO<sub>2</sub>, in addition, adjuvant therapy is performed which consists of an intralesional bevacizumab injection on surgical site. Adjuvant therapy involves a cycle of four intralesional bevacizumab injections. The RRP is characterized as a long-life condition of the respiratory epithelium caused by the human papilloma virus (HPV), HPV 6 and 11 genotypes in most of all cases. Airway obstruction or voice correlated symptoms are the most common way of presentation, which can be variated from a low-mild form to severe which can represent, in rare cases, a situation that requires prompt treatment. This study aims to evaluate the efficacy and safety of the use of intralesional bevacizumab as adjuvant therapy in the treatment of RRP.

**Keywords:** Airway obstruction, Bevacizumab, HPV, Laryngology, Laser, Oncology, Surgery.

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## BACKGROUND

Recurrent respiratory papillomatosis (RRP) has a good tropism to the respiratory ciliated mucosa of the larynx, trachea, and, in some cases, bronchi and lung parenchyma. It is a disease with a worldwide distribution and a very large spread of population, adults, and children (juvenile form). It is a rebellious and capricious disease that exposes the patient to numerous therapeutic interventions, surgical and otherwise. Associated comorbidities can pose a serious threat to the patient's own life, the goals are focused on maintaining airway patency and voice quality.

## CASE DESCRIPTION

A 47-year-old woman, a smoker of 10 cigarettes/day, came to our Otorhinolaryngology department referring hoarseness and phonasthenia for the last three years. In 2005 had surgery for a chordal polyp, in 2007, 2010, and in 2014 had surgery for RRP not well precised. The patient was in a follow-up period in another Otorhinolaryngology department of another university hospital. We performed a fiberoptic laryngoscopy examination with a flexible optic showing a mammellonate neoformation on the surface of the right true vocal cord with an invasion of the anterior commissure and the anterior third of the contralateral true vocal cord (Fig. 1).

Laryngoscopic examination with a 0°, 30°, and 45° rigid endoscopic detected the presence of a mammellonate neoformation in the whole of the right true vocal cord until it touches the anterior commissure and the anterior third of the left true vocal cord. Anterior subcommissural encroachment is suspected. A bicordal normomotility and a reduced respiratory glottic space are also highlighted. Derkay staging system anatomical score marks 12 (3-2-2-3-2). The patient marks a voice handicap index (VHI) score of 75 on 120, a serious handicap impairment.

## TREATMENT

We decided to perform a direct microlaryngoscopy CO<sub>2</sub> laser with the exeresis of the neoformations that involves both vocal folds and

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**Conflict of interest:** None

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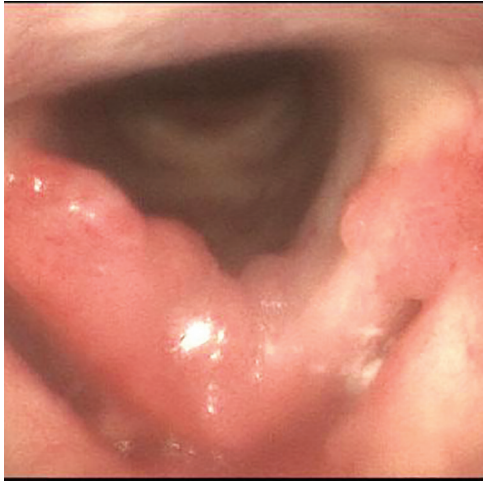
the anterior commissure, at the same time a vaporization CO<sub>2</sub> laser of the free margins of both vocal folds is done. The histopathological diagnosis was squamous papilloma with lobular intraepithelial neoplasia LIN 2, the genotype with reverse line Biot identifying were the 6 and the 66 genotypes.

After ethical committee consent and patient approval, we decided to perform a cycle of four intrachordal bevacizumab infiltrates using a laryngeal needle to inject a 7.5–12.5 mg (0.3–0.5 mL) into the areas affected (Fig. 2).

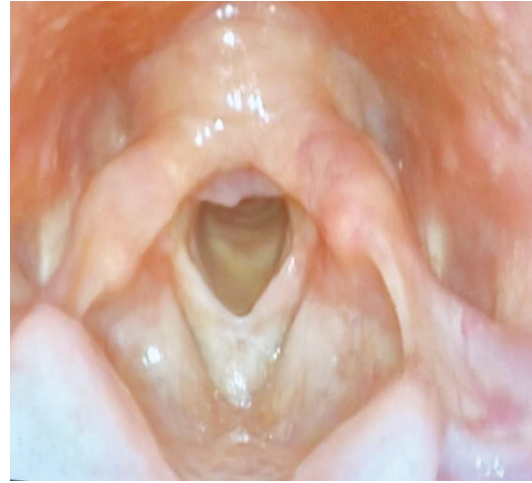
The patient is discharged with a precise therapeutic protocol, based on a 40-mg tablet of esomeprazole before breakfast for 30 days, and chondroitin sulfate, hyaluronic acid, and aluminum hydroxide oral stick after main meals up to the first follow-up visit, antibiotic therapy with 500-mg tablet of azithromycin for three days, and 700-mg tablet of bromelain for 30 days. The patient underwent a cycle of other four bevacizumab injections 3 weeks apart. The goal is to eradicate the RRP. After every bevacizumab injection, two control visits with fiberoptic laryngoscopy are established: the first on the day after the injection, and the other two on 14 days after the other.

## OUTCOME AND FOLLOW-UP

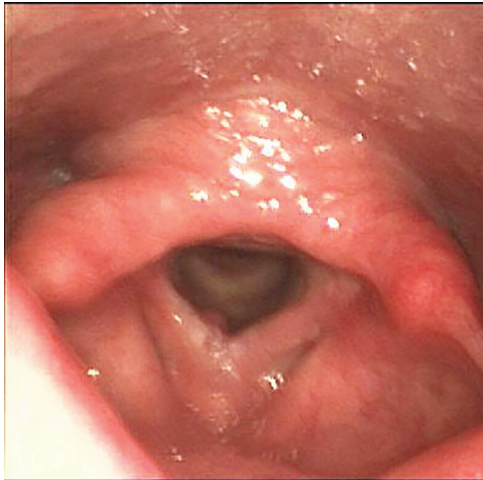
The last follow-up visits performed showed complete eradication of papillomatosis: the vocal fold epithelium appears intact and



**Fig. 1:** Preoperative fiberoptic laryngoscopy examination with a flexible optic showing a mamillated neof ormation on the surface of the right true vocal cord with an invasion of the anterior commissure and the anterior third of the contralateral true vocal cord



**Fig. 3:** Fiberoptic laryngoscopy examination with a flexible optic on the last follow-up visit. The vocal fold epithelium seems intact and normotrophic with a small anterior synechia



**Fig. 2:** Fiberoptic laryngoscopy examination with a flexible optic after the second injection of bevacizumab. The vocal fold epithelium appears intact and normotrophic with a small anterior synechia and a presence of a little chordal polyp on the right vocal fold

normotrophic with a small anterior synechia (Fig. 3). To evaluate the motility, we performed a laryngeal stroboscopic examination showing a preserved vocal cords motility. Her VHI registered marks 10 on 120, low handicap impairment score.

Given the good outcomes of the treatment after the last injection cycle, it was decided to schedule a control visit with fiberoptic laryngoscopy at the sixth month to evaluate the outcome of the therapeutic strategy adopted.

## DISCUSSION

RRP is caused by the human papillomavirus, in particular by subtypes 6 and 11, is one of the most frequent diseases of the respiratory tract in children and adults in the United States. It has been estimated that his frequency is around 4.3 for every 100 000 children and 1.8 for every 100 000 adults, and it has been evidenced how the human papilloma virus is one of the most important risk

factors associated with dysphonia and dyspnea. The literature shows how RRP is a very capricious and rebellious disease due to its characteristic to reappear due to its index of cellular proliferation. The viral genome remains in the cellularity of tissues infected, this is the cause behind the recurrences of RRP. Mostly, due to an unpredictable course of the disease, RRP would need many surgeries to preserve airways permeability.<sup>1-4</sup>

Many surgical approaches are supported by the literature to restore the permeability of the upper airways. Nevertheless, there is no definitive cure. The goal of all surgical approaches must be the preservation of the anatomic structure of the larynx and at the same time maintenance of vocal function and the permeability of upper airways. The microdirect laryngoscope or endoscopic laryngoscopy with the implication of laser, microdebrider, and cold instruments are the most common surgical approaches implicated in the treatment of RRP. We can apply different types of laser, including laser CO<sub>2</sub>, KTP, and pulse dye.<sup>5-8</sup>

Due to his important tendency to recurrences, adjuvant therapy is often offered to the patient with RRP. It is estimated that 20% of patients need adjuvant therapy associated to control the advance of RRP. Actually, in the literature, we can count on many drugs implicated in the treatment of RRP such as Gardasil (Merck and Co, Inc., Whitehouse Station, NJ, USA), cidofovir (Vistide, Gilead Sciences, Inc. Foster City, CA, USA), bevacizumab (Avastin; Genentech/Roche, San Francisco, CA, USA), mumps vaccine, cimetidine, ribavirin, photodynamic therapy, aciclovir, propranolol, and indol-3-carbinol. The main goal of adjuvant therapy is to control disease course. The efficacy of the adjuvant therapy remains uncertain, due to the unpredictability of the tendency of the RRP in each patient.<sup>9-14</sup>

In the last years a great progress in the management of RRP occurred. Cidofovir is the most studied intralesional adjuvant therapy, in addition bevacizumab has recently been documented. Zeitels et al. showed how bevacizumab, an antiangiogenic agent, decrease the volume of the disease when it is used with the KTP laser, with a reduction in recurrency in 90% of treated patients.<sup>15-19</sup>

In consideration of the unpredictability of RRP, the prognosis and possible surgical interventions, the primary therapeutic

objective of this study was to show us how a combined approach, laser surgery and the adjuvant therapy with intralesional bevacizumab reduces or eliminates the need for recurrent surgeries. We also consider as efficacy parameter the remission and recurrence rate, surgical interval free from disease and Derkay scores elevated before and after the therapeutic approach. The VHI is a responsible form for observe voice-related quality of life in patients with laryngeal papillomatosis and correlates with the severity of the disease in the larynx.<sup>20-21</sup>

In our case report, treatment with intralesional bevacizumab seems to be safe and that pharmacologic antiangiogenesis is successful in treating RRP and that it seems to be relatively secure locally and systemically. It is clear that a larger patient cohorts and multi-institutional studies are needed.

### TAKE-HOME MESSAGES

- Intralesional use of bevacizumab, it is valorated as a good adjuvant action in RRP, showing a good results in the complete remission of the disease.
- The literature shows how local intralesional bevacizumab injection is safe despite high cumulative dose was administered.
- Treatment with intralesional bevacizumab is effective in treating RRP and that it seems to be relatively secure locally and systemically. It is clear that a larger patient cohorts and multi-institutional studies are needed.

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