



# Phonosurgery debulking and pharmacological treatment of human papillomavirus patient with recurrent respiratory papillomatosis and vocal outcomes

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**Abstract:** We are presenting this case, a 56-year-old woman, with laryngeal papillomatosis involving both vocal cords and anterior commissure, treated with cold phonosurgical debulking and laser CO<sub>2</sub> surgery, with respect to the mucosa of anterior commissure, and cidofovir and indole-3-carbinol, in order to explain the physiopathological principles of the treatment, the surgical methods and the long term results (8 years and 6 months) in absence of sequelae and vocal outcomes.

**Keywords:** Phonosurgery; laser CO<sub>2</sub>; cidofovir; indole-3-carbinol (I3C); recurrent respiratory papillomatosis (RRP); vocal outcomes

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## Introduction

The recurrent respiratory papillomatosis (RRP) is characterized by the proliferation of squamous epithelial benign cells infected by the virus in the epithelium of the aerodigestive tract and especially in the larynx.

Human papilloma virus (HPV) is the causative agent. Over 90 HPV types have been identified and divided into two main groups according to the probability of determining cancer. They are further divided into subgroups according to genetic similarities, target tissue and carcinogen power. In 90% of recurrent laryngeal papillomatosis cases it is detected the presence of one of two types of subgroup 6–11 belonging to the group with low probability of determining malignant transformation of infected cells. The low expression of P53 isoforms in benign papillomas suggest the low probability of malignant transformation of this lesions (1).

The viral infection may precede the clinical manifestation of several years, it appears as sessile or pedunculated masses, in the average size of about half a millimeter.

The most common site for RRP by far is the larynx, where a squamociliary junction is formed and then usually in the Morgagni's sinus where the squamous non-keratinized epithelium of the true vocal cord meets pseudostratified ciliated columnar epithelium, typical of the respiratory tract.

The most significant aspect of the disease is the high frequency of recurrence after surgical treatment, which makes it extremely disabling and dangerous because the patient will recurrently experience episodes of dysphonia and in some cases dyspnoea, up to especially in children to cases of suffocation; moreover, there are cases in which the surgical interventions, both of cold exeresis and laser vaporization, must be performed even monthly and despite all the evolution of the disease can be very irregular, so it is not rare that the subjects affected by RRP they can go through phases of depression.

In our study we will present a case of surgically treated RRP with cold debulking of the esophitic lesions and low-power CO<sub>2</sub> laser to respect the profile of the vocal cords



**Figure 1** Diagnosis of RRP by laryngoscopy (4). RRP, recurrent respiratory papillomatosis.

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**Figure 2** RRP surgery by cold debulking, laser CO<sub>2</sub> and Cidofovir infiltration (5). RRP, recurrent respiratory papillomatosis.

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and of the anterior commissure as much as possible. Given the various studies in the literature, confirmed by the most recent literary reviews (2), to avoid the high rate of recurrence of the disease we injected the antiviral cidofovir at the wound sites (topical treatment) after surgical treatment and administered orally to the patient indole-3-carbinol (I3C), a derivative of cruciferous which slows down viral replication.

## Case presentation

### Patient selection and workup

A 56-year-old woman, non-smoker, referred progressive dysphonia for 8 months, mild sensation of dyspnea in the supine position for some weeks and absence of dysphagia; during the first diagnostic assessment (5 July 2010) she was submitted to laryngeal videostroboscopy (videoscope Xion), voice self-assessment (VHI-10), GRBAS perceptual voice analysis for deviant voice quality evaluation tests and maximum phonation time evaluation (MPT).

Laryngostroboscopic examination highlighted a papillomatous lesion framed in stage 3, G3b according to Pontes *et al.* grading system (3) (Figure 1). Self-assessment test VHI-10 index: 32; GIBAS: G2 I1, R2, B2, A2, S2; MPT: 6 seconds.

In suspected laryngeal papillomatosis, the suggested treatment protocol was phonosurgical debulking, intra- and peri-wound infiltration with cidofovir and oral therapy with I3C. The patient was informed about the importance of the monthly follow-up and about the possibility for a retreatment in relation to future clinical outcomes until a

final infiltration to 4 months after the last treatment without recurrence;

### Pre-operative preparation

After a complete explanation about treatment, the patient provided a written informed consent and she was scheduled for treatment; she also signed a consent for the use of cidofovir ("off label") according to a protocol approved by many international ethics committees.

All surgical procedures were performed in MLDS (Microdirect Laryngoscopy Suspension) and general anesthesia.

The follow-up predicted laryngostroboscopic examination, performed by video nasopharyngoscope EV-N Xion connected to EndoSTROB DX, Matrix Ds data station with DIVAS video analysis and archiving software or video endoscope Olympus OTV-SI Digital Processor (ENF TYPE V2), connected to an external KAY RLS 9100 B RHINO-LARYNGEAL STROBOSCOPE, VHI-10 index, GRBAS perceptual voice analysis, performed simultaneously by three doctors, spectrographic voice test using Xion or Kay and maximum phonation time (MPT).

### Procedure

On August 5th 2010 the first surgical session was done (Figure 2).

The proposed and applied treatment protocol was the following:

- (I) General anesthesia with 6 mm ID rhino-tracheal



**Figure 3** Follow up after 7 years and 6 months by laryngoscopy (7).  
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- (II) tube placement to facilitate surgical maneuvers;
- (II) Exophytic lesions debulking with cold instruments saving as much as possible both the cordal mucosa and the lamina propria;
- (III) Extemporaneous evaluation of the lesion, confirmation of papillomatosis diagnosis and final assessment with viral typing (HPV6);
- (IV) Careful inspection of papillomas anatomic site, often corresponding to the squamociliary junctions in which ciliated and squamous epithelia are juxtaposed, through surgical sponges put in surgical nippers which can also be left in place so to lift papillomas (third hand) and to facilitate the dissection performed through Bouchayer grasping forceps with suction;
- (V) Treatment of papillomas in anterior commissure with resolution and control of synechiae: after placement of a self-retaining laryngeal retractors, the anterior commissure was treated with the same methods used for the remaining chordal portion; in order to treat and avoid to worsen the synechia of the anterior commissure, the free edge of the chordal profile, near the commissure, will be respected even if in presence of papillomatous formations; the power of the CO<sub>2</sub> laser will be utilized at low energy, directed to the upper surface of the vocal cord, in order to determine a mucosa retraction of the upper side of the vocal cord with consequently epithelial coverage of the free edge.
- (VI) Intra and perilesional infiltrations of cidofovir, both in the mucosal with pathological aspect and in the adjacent mucosa, because of the virus can

dwelt in macroscopically unharmed cells;

- (VII) Rigid Endoscopic Surgery Microlaryngeal (REMS) enhances the ability to assess a more precise control and infiltration in all mucosal laryngeal areas—even in regions that are hidden to a microscopic vision;
- (VIII) Endoscopic control to 24 hours, with serological tests that have always ruled out any hepatotoxic or nephrotoxic effects of intralesional cidofovir;

Cidofovir was administered according to the following scheme: concentration of 5 mg/mL with infiltration of 2–3 mL per session for a total of 3 sessions with intervals of 4 weeks between first and second session and 4 months between second and third session. Infiltration was always performed in MLDS and under general anesthesia.

### Post-operative management

During the first treatment the following therapy was undertaken: I3C, 400 mg/day for the first month and 200 mg/day for 2 months. I3C is a phytochemical substance, present in cruciferous, which plays an antioxidant, anti-cancer action and inhibits HPV proliferation in cell cultures (6).

The patient was submitted to close follow-up with monthly checks for the first 3 months, then every 2 months for 12 months and finally for 4 times a year.

All checks have not highlighted relapses and the voice quality is steadily improved (*Figure 3*: control at 7 years and 6 months) with the following values at the last 7 years and 6 months' control after surgery: VHI-10 1, GIRBAS: G0, I1, R0, B0, A0, S0, MPT: 18 seconds and spectrogram type 1 according to Yanagihara principles modified by Ricci Maccarini, confirming the protocol effectiveness.

### Discussion

Important implications for therapeutic management:

- (I) HPV infects only epithelial cells (never the connective cells), inducing proliferation;
- (II) HPV is localized also in epithelial cells of normal appearing-mucosa adjacent to the lesions, persisting in epithelial cells even during the quiescent phases of the disease: the mere presence of the virus in the cell is not sufficient for disease and requires further triggers of immune, traumatic, viral and hormonal nature still not well known, which are able to activate cell proliferation.

These findings suggest that surgical treatment should be aimed at removing papillomas and not the virus: more aggressive treatments do not improve the control of relapses, but predispose to laryngeal permanent sequelae such as stenosis, granulomas formation and alterations of the fine dynamic phonatory of vocal cords with permanent dysphonia.

Different treatment modalities have been described for the recurrent laryngeal papilloma; in the literature encouraging results have been reported by the use of an antiviral agent cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine], a cytosine nucleotide analog, that can selectively inhibit viral DNA polymerases during viral replication, approved by the US Food and Drug Administration for systemic use in the cytomegalovirus retinitis treatment among HIV/AIDS patients (8). It is able to inhibit tumoral growth of epithelial cells induced by HPV. In 1995 Snoeck *et al.* (9) first demonstrated the cidofovir efficacy in humans, in individuals with genital HPV treated with local gel formulations. In the same year Van Custem *et al.* (10) injected directly cidofovir in hypopharyngeal and esophageal lesions; in 1998, Snoeck *et al.* (11) published good results on a set of 17 patients, with recurrent laryngeal papillomatosis, treated with local injections of cidofovir; since then, several studies have shown the cidofovir efficacy in recurrent papillomatosis treatment without detection of local or systemic side effects. On the other hand, other studies (12) criticize the results effectiveness by reporting only a partial benefit of the use of intralesional cidofovir in association with surgery.

Limitations in published studies regard the homogeneity of treated patients (usually already submitted to multiple not definable interventions), the absence of control groups (control groups are not justifiable, if considering cidofovir effectiveness versus placebo and the upgrade of the disease), the absence of shared protocols, the timing and spacing of doses, the maximum feasible dose in a patient, the effects of CO<sub>2</sub> surgery (13) and the description of surgical procedures performed.

The case report describes the pathophysiological basis of a therapeutic phonosurgical protocol combined with therapy and reports results in absence of recurrence and voice outcomes in a follow-up of eight years and six months of an adult patients with a first diagnosis of HPV6 laryngeal papillomatosis in stage 3 G3b by Pontes *et al.* grading system (3), therefore never submitted to previous interventions.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jovs.2018.06.24>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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