Can Mumps Vaccine Induce Remission in Recurrent Respiratory Papilloma?

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Objective: To describe our experience using laser excision and locally injected mumps vaccine to induce remission in patients with recurrent respiratory papilloma (RRP).

Setting: Tertiary care regional medical center.

Participants: Initially, 11 children with RRP treated in a pilot study with laser excision at regular intervals for at least a year without adjuvant therapy; later, a series of 18 children and 20 adults with RRP, some of whom had used various adjuvant therapy with interval laser excision.

Interventions: Both patient groups continued their same interval laser excision with the same or similar laser, same clinical setting, and same surgeon. Locally injected mumps vaccine was then administered into the excision site after each laser removal of papilloma.

Outcome Measures: Larynx and trachea were microphotographed with each treatment. Two consecutive disease-free intervals and a follow-up of at least 1 year were required criteria for remission.

Results: In the pilot study, remission was induced in 9 (82%) of 11 patients by 1 to 10 injections, with follow-up of 5 to 19 years. In the subsequent series, remission was induced in 29 (76%) of 38 patients by 4 to 26 injections, and follow-up was 2 to 5 years.

Conclusions: Combined with serial laser excision, mumps vaccine positively influences induction of remission in children with RRP. The mechanisms of this effect are unclear, but the treatment is readily available, inexpensive, and has a low risk of adverse effects.


Recurrent respiratory papilloma (RRP) is a protean disease caused by infection with the human papillomavirus and for which there is currently no single effective treatment. In children, frequent surgical removal is common to maintain an airway. Adults and children suffer loss of voice and, in aggressive cases, a tracheostomy is sometimes required. Tracheal seeding and lung involvement can occur with fatal outcome.

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Recurrent respiratory papilloma is rare (254-763 US children affected per year) but may cost $40 million to $123 million annually. It also is the most common benign laryngeal tumor in children. Papillomas may develop in any mucosal area of the aerodigestive tract, with the vocal cords the most commonly affected site. Why this particular site is so consistently involved is unclear, but from the various adjuvant treatments tried, there is implied agreement that a local immunocompetence to the viral agent may be present in susceptible patients. A variety of adjuvant therapies for RRP have been tried with varying success, including interferon alfa, photodynamic therapy, indole-3-carbinol, acyclovir, retinoic acid, cidofovir, topical fluorouracil, and Thuja, a homeopathic antiviral preparation.

Surgical removal has evolved from debulking with cup forceps, which is still useful, to the more standard use of the laser and microscope. This latter treatment allows precise removal but is not without the risks of scar, webbing, and stenosis. Rarely, fire from inadvertent endotracheal tube ignition has occurred, with tragic outcome, and many surgeons have adopted a proximal jet ventilation technique that reduces this hazard. Excision using a microdebrider has also been tried by some surgeons, and with the recurrent nature of the disease, some surgeons set regular intervals for patients to return for laser endoscopy. This approach aims to keep the airway open and maxi-
METHODS

My first use of mumps vaccine as RRP therapy (in 1980) and my second use (1989) were 9 years apart. Both resulted in spectacular remission, and a pilot study was then prospectively undertaken in 9 patients who, without much change in their recurrence interval, had been under treatment for at least a year. The results in these first 11 cases were encouraging enough to continue using this off-label treatment in a subsequent group of patients. No patient agreed to participate in a prospective blinded trial, even though crossover would have ensured that all participants could have eventually received mumps vaccine. This report should therefore be considered as preliminary. Additionally, there were no controls.

Each patient was treated with laser vaporization of papilloma in an identical manner at a treatment interval determined by the extent and severity of their disease. I used a prospective approach to recurrence, shortening the treatment interval when recurrence increased in extent, and lengthening it when recurrence had diminished. Photography through an endoscope and an illustration by the surgeon were used for retrospective analysis of disease severity. No phenotypic analysis of the causative virus was performed. The criteria for remission were at least 2 consecutive disease-free intervals, with a follow-up of at least 1 year.

I used proximal jet ventilation through a custom-made suspension laryngoscope (Sontec, Denver, Colo) to apply laser vaporization to affected areas after removal of tissue for histologic examination by cup forceps. Settings were 2 to 5 W with a spot size of 0.5 to 0.75 mm and continuous mode on a carbon dioxide laser (Coherent, Santa Clara, Calif). In the last 2 years, I have used a carbon dioxide laser (SSI Laser Engineering, Nashville, Tenn) with an “ultrapulse” mode, which provides a 40-microsecond pause between energy bursts and allows tissue cooling and less char. I still use 2 to 5 W of energy, but the spot size is smaller at 0.1 to 0.2 mm. To open the ventricle in the adult patients, a larger custom laryngoscope (Sontec) was made.

Each ampule of mumps vaccine was initially reconstituted to 2 mL. (the needle for infiltration has a dead space of 0.5 mL) and injected into the tissue at the base of the site of laser excision of any papilloma using microscopic control and a laryngeal injection needle (Piling Co, Philadelphia, Pa) with a working length of 30 cm. From my experiences with adult patients, I theorized that their response to treatment with mumps vaccine was related to the number of ampules administered. The dilution of each ampule was reduced to 0.5 mL to allow the number of ampules injected with each treatment to be increased, and this is my current technique in adults and children.

No oral or parenteral steroid medication was used during or after laser therapy despite the presence of (injected) edema. This was based on my supposition that any steroid administered might be immunosuppressive; it is important that all treating staff, particularly the anesthesiologist, be alerted to this. Edema or bleeding intraoperatively was managed by the use of topically applied 0.25% phenylephrine on a cotton pledget. After the mumps vaccine was injected, virtually complete occlusion of the airway was common. This was managed by gentle suspension of the airway for a few minutes, using the laryngoscope or a bronchoscope, but neither was forced into the airway, and commonly a topical application of racemic epinephrine was used. This can be applied by direct instillation of a measured dose based on weight, with the larynx suspended, or by nebulized droplets in a postanesthesia recovery unit.

RESULTS

INITIAL PATIENTS

In 1980, the first patient for whom I used mumps vaccine as a treatment for RRP was a 5-year-old girl who, after 3 years of regular laser treatment, suddenly saw her treatment interval shorten from every 6 weeks to every 14 days. A single intralaryngeal immunization into the base of the lasered area was used, and immediately the patient was able to revert to a 6-week treatment interval. With 3 subsequent intralaryngeal injections at the time of laser removal of papilloma, there was complete remission. This was not immediately apparent, however, because there was a 6-year interval between the last treatment and the next contact for treatment of a small anterior web causing hoarse voice. This patient remained in remission as of December 2000.

The second patient presented for treatment at age 1 year and initially was treated at intervals of 3 to 5 weeks. At age 2½ years, there was gradual worsening, shorter intervals between surgical procedures, several increasingly longer episodes of respiratory support by intubation after laser excision of papilloma, scar formation with recurrent mimize the voice while avoiding tracheostomy. The treatment interval can be shortened or lengthened as needed.

Although spontaneous remission is alleged to occur, I have never seen it. Accurate reporting of the varied therapies used has been improved by the adoption of a scoring system proposed in 1998 by Derkay et al. This allows the surgeon to stage and/or score a patient’s disease manually or directly into a computer. The operating surgeon assigns a score of 0 to 3 where 0 indicates no lesion; 1, surface lesion; 2, raised lesion; and 3, bulky lesion. Four questions about voice, stridor, the urgency of that day's operation, and my second use (1989) were 9 years apart. Both resulted in spectacular remission, and a pilot study was then prospectively undertaken in 9 patients who, without much change in their recurrence interval, had been under treatment for at least a year. The results in these first 11 cases were encouraging enough to continue using this off-label treatment in a subsequent group of patients. No patient agreed to participate in a prospective blinded trial, even though crossover would have ensured that all participants could have eventually received mumps vaccine. This report should therefore be considered as preliminary. Additionally, there were no controls.

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when I switched from using the Coherent carbon dioxide laser to the SSI carbon dioxide laser equipped with ultrapulse. If necessary, up to 9 ampules of mumps vaccine diluted to 4.5 mL were later used for each treatment. Eighteen of the 38 patients had previously used some adjuvant therapy, and 4 continued to use indole-3-carbinol during our treatment. No patient had used interferon within the past 2 years prior to our treatment.

Histologic examination of papillomas from all patients revealed benign squamous papilloma with mild atypia and koilocytic changes and changes typical of viral-induced papilloma. As remission was induced in patients, biopsy specimens did not demonstrate any particular change; ongoing mild acute and chronic inflammation was present in all patients at some stage in their illness. Biopsy specimens from areas where complete remission had been induced showed fibrosis, but these specimens were not consistently taken because taking them in some instances could have adversely affected voice quality. Additionally, these areas were often difficult to locate by the time of the next treatment. No phenotyping of papilloma was undertaken.

### Table 1. Pilot Study Group

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Severity Score</th>
<th>Mumps Vaccine</th>
<th>Laser Interval, wk</th>
<th>Present Status</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>No. of Ampules</td>
<td>Amount, mL</td>
<td>No. of Injections</td>
</tr>
<tr>
<td>1/3/3</td>
<td>23</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>3/3/3</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>3-11/5 F–8 M/0.8-8</td>
<td>18-24</td>
<td>3-6</td>
<td>1-3</td>
<td>1.5-5.5</td>
<td>1-10</td>
</tr>
</tbody>
</table>

*A total of 9 (82%) of 11 patients are in remission.

### Table 2. Subsequent Group Results for Children and Adults

<table>
<thead>
<tr>
<th>No. of Patients/</th>
<th>Severity Score</th>
<th>Mumps Vaccine</th>
<th>Laser Interval, wk</th>
<th>Present Status (%)</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/Age, y</td>
<td>Before</td>
<td>After</td>
<td>No. of Ampules</td>
<td>Amount, mL</td>
<td>No. of Injections</td>
</tr>
<tr>
<td>18/10 F–8 M/1-11</td>
<td>18-26</td>
<td>1-11</td>
<td>1-6</td>
<td>1.5-12.5</td>
<td>4-26</td>
</tr>
<tr>
<td>20/20 M/19-57</td>
<td>19-28</td>
<td>0-9</td>
<td>3-9</td>
<td>5.5-15.5</td>
<td>4-20</td>
</tr>
</tbody>
</table>

**COMMENT**

Local infiltration of mumps vaccine, when combined with serial, prospective laser excision of respiratory papilloma to maintain airway and maximize voice, is capable of improving the remission rate. It is not clear how this occurs, and there are a number of variables, none of which is truly addressed in this report. After initial excision and injection, the placement of injected liquid around remaining papilloma in the larynx provided a much improved view of the tissue separation and less collateral thermal injury when the laser was used, and an improved clearance was achieved. The removal of papilloma at the apparent point of origin was therefore possible with this method, but I have not attempted this with saline or other liquid. No phenotyping of papilloma was undertaken in any of my patients because of the lack of apparent clinical correlation reported.

**PILOT GROUP**

Retrospective severity scores before treatment of these 2 patients under the schematic suggested by Derkay et al were 23 for the first and 25 for the second. After treatment, each patient had a severity score of 1. These 2 original patients were observed at regular intervals, and a pilot study was undertaken to see if their results could be duplicated. A total of 9 consecutive patients, aged 18 months to 8 years, who had been under treatment for at least a year by the same surgeon using the same laser endoscopic equipment at regular 3- to 12-week intervals, were prospectively treated with locally infiltrated mumps vaccine at each regularly scheduled suspension laryngoscopy (Table 1).

**SUBSEQUENT SERIES**

The subsequent treatment group consisted of patients who had requested mumps therapy with their regularly scheduled laser debulking. A total of 38 patients (16 female and 22 male), including 18 children aged 1 to 11 years and 20 adults aged 19 to 57 years, were treated at the same regular interval of treatment that had been established prior to introduction of the mumps vaccine therapy (Table 2). Treatment was altered slightly for some of these patients when I switched from using the Coherent carbon dioxide laser and later tracheostomy with the development of peristomal papillomata infiltrating the skin. Interferon was used 4 times without discernible effect. This was the only patient in this group to receive adjuvant therapy other than mumps vaccine. A single intralaryngeal injection of mumps vaccine produced marked flattening of intralaryngeal papilloma and loss of a bulky papilloma in the right main stem bronchus without laser removal at this site. Five serial injections at 3- to 5-week intervals, including infiltration of the skin within the tracheal stoma, produced complete remission. A laryngotracheoplastic reconstruction of the patient’s stenotic subglottis was then possible, and decannulation successful.
During the follow-up of this small series of patients, the following observations have helped modify our approach. In all patients, the lateral posterior ventricle was the last site where papilloma was found and eliminated other than the anterior commissure. In patients who had persistent hoarseness without obvious papilloma, it was the rule to see scar partially or completely webbing the ventricle (bridging from the false to the true cord). An incision laterally into the ventricle often resulted in uncapping of a mucus-containing microcyst with papilloma within it. Opening the ventricle, therefore, might be essential if complete remission is to be achieved. Some modification of the severity score might be appropriate in this area, which is not a separately named area in the published assessment.

The results from the pilot study group would indicate that the apparent improvement in remission rate for these patients was not simply due to the better or more complete removal of their papilloma when liquid was placed into the tissue spaces. All of these patients had been receiving the same treatment by the same surgeon using the same equipment and approach for at least 1 year, and the only variable was the introduction of mumps vaccine.

Two patients in the subsequent group, both younger than 1 year, required only 1 injection of mumps vaccine for the induction of complete remission. Neither patient had been immunized with a measles-mumps-rubella (MMR) vaccine. Additionally, 3 other patients in this group went into remission despite papilloma at sites within the trachea that were not directly infiltrated with mumps vaccine. Four parents of affected children have independently suggested that the timing of their child’s obstructed airway coincided with their 1-year immunization with MMR vaccine. Each of these patients had altered voice from the neonatal period but had not sought medical attention until the airway suddenly became more obstructed after their immunization. This suggests that an agent in the MMR vaccine triggers an inflammatory change in respiratory papilloma growing harmoniously in the airway of children with RRP. The numbers here might be at the anecdotal level, but it is difficult to deny that there may be an effect that is not caused solely by improved ability to remove the papilloma at a local site but is the result of a systemic, probably immune, agent.

The adult patients in our series do not seem to be a recognizable difference in clinical group. Their disease in some cases had been present for a shorter time than in the pediatric group, but in others, longer, and 2 adult patients were childhood papilloma “graduates” with persistent papilloma. Interestingly, most of the affected adults older than 40 years had not been immunized against measles, mumps, or rubella in childhood and had immunity only from acquiring the diseases.

Although it would be interesting to measure the patients’ antibody response to the repeated mumps vaccinations, I have not done so. The quantity of vaccine given varied not only by patient size and area of papilloma involvement, but by frequency of injection and simple tolerance of the larynx to what is essentially directly injected edema. My approach was to inject to the point of tolerance. My impression is that the more extensive the papilloma, the greater the “antigen load,” and the more vaccine is required to see an effect. However, the present report does not analyze this impression, and it is unknown whether a threshold amount of mumps vaccine has to be given before an effect is seen. It is also unknown whether the remission effect is related at all to the amount of antigen or papilloma present. Nor have I compared the patient’s baseline lymphocyte count (T cells and in particular natural killer cells) with that of a population without active or previous infection with the papilloma virus. However, the successful use of an off-site immunization with a proven track record against 1 virus to treat a viral infection caused by a different category of virus in another anatomic location might imply stimulation of the patient’s own impaired immunity to viruses in that location.

Interestingly, the mode of administration of mumps vaccine used in the present study is identical to that described by Pransky et al with intralesional cidofovir to induce remission in patients of similar age with the same disease. The remission rate is also strikingly similar in their series of patients, and they too discussed the patient’s ability to “mount an adequate immune response to HPV [human papillomavirus] once the tumor burden is decreased.” We may be approaching this disease by similar methods from 2 opposing directions. Cidofovir treatment might reduce the tumor burden locally to the point at which the patient’s own immune is able to function; and the mumps vaccine might be stimulating the immune system systemically to the point of competence for this particularly pernicious virus. Clearly there is much research to be performed before clear answers are available.

Coincidence is also a possibility, but intralesional mumps vaccine is safe, readily available, easy to use, and, at a cost of approximately $25 per ampule, inexpensive to administer. If the results of the present report can be duplicated by other surgeons, further study of possible mechanism of action might provide aid for this group of patients.

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REFERENCES