Commentary

Total Laryngeal Transplant Explanted: 14 Years of Lessons Learned

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Abstract
In 1998, the first successful total laryngeal transplant was performed. Outstanding voice quality and swallowing function were achieved, and over the subsequent 14 years, much was learned about tolerance of a transplanted larynx. After approximately a decade, a slowly progressive, chronic rejection process gradually rendered the organ nonfunctional, and the patient and his providers deemed him appropriate for explantation. This is a report of the clinical indications and outcome surrounding the explantation of the first successful total laryngeal transplant.

Keywords
laryngeal transplantation, larynx transplant

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Introduction
In 1998, the first successful total laryngeal transplant was performed by a team led by the senior author. The patient was a 40-year-old man who had suffered an MVA 20 years prior that left him aphonic. Not only was his larynx completely replaced with a vascularized graft, but also his pharynx, thyroid, parathyroids, and a portion of his trachea. After approximately a decade, a slowly progressive, chronic rejection process gradually rendered the organ nonfunctional, and the patient and his providers deemed him appropriate for explantation with free-flap reconstruction and TEP voice restoration.

Case
Details of the original transplantation as well as interim reports have been detailed in the literature previously, including a published update at the twelfth year after transplant.1-4 During that twelfth year, the patient developed a mucosal lesion in the postcricoid area, which did not respond to IV antibiotics. Biopsy and debridement of the area demonstrated ulceration, granulation tissue, and acute inflammatory cells with bacterial overgrowth, without evidence of fungal or viral infection. Although an extended course of IV antibiotics gradually improved the ulcerative area, the patient’s voice quality and discomfort progressively worsened. By the fourteenth year after transplantation, the patient’s function had decreased to the point of contemplating explantation. He suffered from bilateral pharyngeal pain that radiated to his ears, as well as deterioration in voice quality, which had become breathy with poor pitch control.

Although minimal levels of immunosuppression had been achieved (prednisone 5 mg qday, tacrolimus 1 mg bid, mycophenolate mofetil 750 mg qAM/500 mg qPM), when medication levels were increased, the pain improved as did the voice quality, which seemed to correspond to decreased edema of the true vocal folds. Unfortunately, as vocal fold edema decreased, the patient’s level of aspiration of liquids increased when drinking. Bilateral injection of calcium hydroxylapatite gel (RADIESSE Voice, Merz Aesthetics) was not able to mediate the stiffened vocal folds. Although not life threatening given his patent tracheostoma, the aspiration became increasingly bothersome to the patient, and without significant voice quality and chronic discomfort, the patient elected for explantation. Routine TEP counseling was performed to assist the patient with the communication transition after explantation.

Immediately prior to explantation, an I-123 uptake scan was performed demonstrating no discernable uptake in the transplanted thyroid and normal uptake confined to the native thyroid lobes. At explantation, the border between native and transplanted pharynx was readily apparent and scarred, while the larynx was noted to be atrophic (Figures 1 and 2), with an absent epiglottis and a necrotic ulcer at the petiole. Histologic examination revealed extensive fibrosis, occlusive vasculopathy, marked acute and chronic inflammation, and acute chondritis (Figure 3). Immunostains on the larynx

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showed a mixed CD3- and CD20-positive lymphocyte population and CD138, kappa light chain, and lambda light chain immunostaining plasma cell population. There was no morphologic or immunophenotypic evidence for a neoplasm in the larynx. The thyroid gland demonstrated atrophy with fibrosis and chronic inflammation, with C-cell hyperplasia (Figure 4). No parathyroid glands were found in the specimen despite their inclusion in the initial transplantation, suggesting atrophy of the donor glands (the patient had never exhibited parathyroid hormonal or calcium abnormalities).

Given the significant pharyngeal augmentation at the time of the original transplantation, reconstruction with an anterolateral thigh fasciocutaneous free-flap was planned. In a portion of the native inferior tonsillar mucosa resected along with transplanted organ, permanent sections revealed an area of squamous cell carcinoma not visible on gross examination. The poorly differentiated but minute cancer was strongly and diffusely positive for p16 and high-risk HPV subtypes (Figure 5). The patient was subsequently taken back to the operating room for a margin-negative resection of the area. No further adjuvant therapy has been administered, and he remains cancer free 12 months after explantation.

Postoperatively, the patient’s immunosuppression was completely weaned, and he has achieved fluid TEP-voice usage. In an interview reflecting on his procedure, the patient states that he had no regrets in deciding to undergo the transplant and was thankful for the opportunity it created for the scientific community to learn from the experience. Reflecting on the advantages the transplant had afforded him, including improved swallowing, taste, and smell, he prioritized the expressive aspects of being able to communicate emotion through voice as the most important quality of life improvement he had experienced through the transplant, and he would accept the opportunity to undergo a second larynx transplant if afforded the opportunity.

Discussion
The experience of this patient is the longest surviving maiden transplanted organ system when immunosuppression was applied. Multiple lessons have been reported based on
this experience in the domains of immunosuppression, laryngeal function, and reinnervation of a transplanted larynx, along with improvements in quality of life. The purpose of this report is to describe the conditions that led to explanation, the findings surrounding the procedure, and the patient’s own perspective on the experience.

Starting around the twelfth year after transplantation, a combination of an infectious and chronic rejection pattern emerged. Since the large, anastomosed vessels to the transplant were noted to be patent at explantation, the cause of the organ failure could have been microvascular occlusive disease, or chronic rejection of the tissue, or a combination of the 2. While the infectious process was able to be controlled medically, the larynx became increasingly stiff and nonfunctional in terms of vocal cord pliability and movement of the laryngeal complex with swallowing. The transplanted thyroid gland, which had demonstrated preferential uptake of Iodine 4 months after the initial transplantation, had become non-avid immediately prior to explantation and was shown to have few remaining follicles on histology.

The discovery of a concurrent cancer of the aerodigestive tract prompts the question of malignant potentiation by the immunosuppressive medications. The authors had always been concerned about this possibility and had performed concurrent animal studies to support altering immunosuppressive regimens that would decrease the risk. Due to the presence of HPV within the malignancy, it will likely be unknown whether this nonsmoker’s male gender and high-risk age group were responsible for the etiology of the neoplasm, while undoubtedly the advantageous timing of the explantation led to the early diagnosis and subsequent treatment, which was nonmorbid and easily tolerated.

Perhaps most important in retrospect is the patient’s own perspective on the experience. Not surprising in our communications-driven modern world, voice quality was the paramount advantage to the patient’s quality of life that the transplant offered. The ability to contribute to mankind’s understanding of disease processes and novel treatments are most commonly attributed to scientists and clinicians, but often overlooked is the ability of individual, volunteer patients to contribute in a meaningful way to the advancement of medicine, which clearly impacted this patient’s decisions. Lastly, probably the most illustrative insight that the patient communicated was the request to be considered for a subsequent transplant should the opportunity arise.

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Author Contributions

Robert R. Lorenz, conception, design, acquisition of data, analysis and interpretation of data, drafting article, final approval; Marshall Strome, conception, design, acquisition of data, analysis and interpretation of data, revising article, final approval.

Disclosures

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