Commentary: When “cutting edge” is “over the line”

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Central Message

Synthetic tracheal grafts seeded with bone marrow cells do not become living, functional trachea but rather fail via dehiscence, fistulization, and obstruction, ultimately leading to patient death.

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The manuscript by Fux and colleagues¹ reports on the long-term outcome and ultimate demise of the 3 patients who received 4 synthetic tracheal grafts seeded with bone marrow mononuclear cells at the Karolinska University Hospital in Stockholm, Sweden, between June 2011 and July 2013. These clinical cases demonstrate that the tracheal grafts not only fail to become epithelialized but that, contrary to previous reports, there is no evidence that these grafts ever resulted in a living, functional trachea but rather unequivocally resulted in protracted futile hospital courses that ultimately resulted in the death of all 3 patients. It is important that the data and clinical course of these patients be known in detail and that the clinical and scientific outcomes be transparent in this controversial field. The detailed data, images, and videos provide clear evidence of the profound failure of these grafts, the absence of epithelialization, and the common themes of anastomotic dehiscence, fistula formation, obstruction, detachment, and infectious complications experienced by these patients, all of which provide useful insights for the field of regenerative medicine and tracheal replacement specifically.

However, this manuscript also forces us to reflect on the ethical challenges and the human costs of the translation of surgical innovation gone awry and the inherent conflict of interest that can arise from academic, social, and monetary incentives for the surgeon, hospital, and cardiothoracic academic community at large. Notably, these synthetic tracheal replacements were done without ethical or regulatory approval by the regional ethical review board at a well-respected academic institution. Instead, each patient was done under a hospital exemption used for compassionate use in critically ill patients. This is particularly troubling, given that the first patient to ever undergo this procedure was a young asymptomatic patient with a low-grade mucoepidermoid carcinoma of the trachea. Multiple biopsies of the graft before implantation failed to demonstrate a cellular lining despite 2 separate bone marrow aspirates, and thus the patient was given supra-therapeutic doses of granulocyte-colony stimulating factor and epoetin-alfa as “regenerative boosting therapy” to rescue the graft that

was implanted nonetheless. The second patient, also asymptomatic at the time of the implantation, developed multiple arterial and venous thrombi in response to the “regenerative boosting therapy,” as did all of the patients. The third patient underwent tracheal replacement at age 22 years to repair an operative tracheal injury that initially occurred during a thoracoscopic sympathectomy. Her hospital course ultimately involved implantation of 2 synthetic grafts, right-sided pneumonectomy, allogeneic tracheal and lung transplant, extracorporeal membrane oxygenation, transhiatal esophagectomy, thoracoplasty, thousands of bronchoscopies, and 57 airway stent interventions. The patient was in an intensive care unit for over 4 and a half years with open wounds, purulent chest drainage, and complex multi-site fistulas. All 3 patients ultimately died secondary to complications of their failed tracheal grafts.

These deaths and the events surrounding the surgeon, Paolo Macchiarini, have been well publicized, but despite the gravity of these outcomes and the devastating morbidity incurred by these patients, several other patients have undergone tracheal graft implants in Sweden, Russia, the United States, and the United Kingdom, with the outcomes less well documented. In reading this manuscript, one will likely also experience the pain, anger, and frustration of the patients, providers, and care team. It is the publication of the scientific truth and clinical reality that that these grafts did indeed fail—profoundly—that is the purpose of the manuscript, with the goal of preventing suffering in other patients. The authors are to be applauded

for helping us face truth even when not a success and for showing us the grave consequences of the siren call of fame to ourselves, our patients, our coworkers, and our profession.

Reference

1. Fux T, Österholm C, Themudo R, Simonson O, Grinnemo K-H, Corbascio M. Synthetic tracheal grafts seeded with bone marrow cells fail to generate functional tracheae: first long-term follow-up study. *J Thorac Cardiovasc Surg*. 2020;159:2525-37.e23.