

Lung transplantation and esophageal dysfunction

Advances in surgical technique, lung preservation methods, reperfusion injury and infection management, and postoperative intensive care have improved survival rates in the immediate postoperative period of lung transplantation; however, subsequent evolution places lung transplants in the group of organ transplants with poorer outcomes, with acute rejection and most commonly bronchiolitis obliterans being cited as major causes of this (1,2). The bronchiolitis obliterans syndrome (BOS) concept has been used to describe post-transplant lung function impairment as unaccounted for by bronchial anastomosis stenosis, infection or acute rejection (1). Time from transplantation to BOS development may range from a few months to several years but mean time to diagnosis is 16-20 months on most occasions. For most patients BOS is a progressive condition virtually unresponsive to enhanced immunosuppression; it is responsible for >30% of all deaths occurring in the third year after surgery (2).

Etiologic factors potentially involved in BOS development include those associated with esophagogastric disease, most particularly gastroesophageal reflux (GER).

The relationship between esophagogastric and respiratory conditions is well supported by epidemiologic data (3), and may occur according to three distinct models – first, some conditions such as systemic sclerosis may entail similar pathogenic mechanisms in the respiratory and digestive systems; secondly, some functional digestive disorders such as reflux may induce various impairments in the respiratory system; finally, in conditions such as chronic obstructive pulmonary disease (4) respiratory changes induce digestive impairments. Not only are these three situations mutually exclusive but they may commonly interact with each other to perpetuate or aggravate lesions.

In patients with end-stage lung disease eligible for lung transplantation GER, esophageal dysmotility, and gastroparesis are highly prevalent, with estimated frequencies of 68%, 76.7%, and 50%, respectively (5-8). Lung transplantation worsens these disorders, and vagus nerve injury, local ischemia, post-surgery esophageal and mediastinal scarring, and autonomic nervous system changes have been involved as potential mechanisms (9).

GER in patients with respiratory conditions has a pattern that differs from the one seen in individuals with severe erosive esophagitis – a higher proportion of reflux in the upper esophagus is found in patients with respiratory symptoms (10).

Multiple reports consider GER a high-risk factor for BOS based on association studies, the potential role of microaspiration as chronic rejection trigger, and clinical evidence of better outcomes in patients undergoing fundoplication (1,11,12); however, some studies have conflicting results, and find no clear association between reflux severity and BOS, poor results with acid secretion inhibitors (13), and inconsistent improvement with fundoplication. All this has led to consider esophageal motor dysfunction a key factor for both reflux development (14,15) and lung allograft rejection (16).

Clinical diagnosis is clearly insufficient in assessing these patients. Neither symptom frequency nor symptom severity allow to predict GER, motor changes, or the presence of an endoscopic lesion (11,13,17).

During the past few years multiple studies were performed in these patients using manometry, pH-metry and other “conventional” techniques, which revealed a high rate of GER and manometric changes such as increased pressure gradient between chest and abdomen, low pressure in the lower esophageal sphincter, and hypomotility disorders in the esophageal body, all of them associated with GER.

Studies using high-resolution manometry and newer endpoints (Chicago Classification, V.3), and the possibility of simultaneous impedanceometry and impedance pH-metry recordings on an outpatient basis represent a significant advance. A more accurate assessment of the esophageal motor behavior and its relationship with the progression of esophageal contents, whether following reflux or deglutition, offers new possibilities for both diagnostic and therapeutic approaches. The study by Ciriza de los Ríos et al., included in this issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* (18), discusses esophageal motor dysfunction in patients with end-stage lung disease both before and after lung transplantation and according to the presence of lung graft rejection. This paper is among the limited number of studies where high-resolution manometry is used. Its results confirm that ineffective esophageal motility is the most common esophageal motor disorder in patients with GERD-related respiratory symptoms (9,19). Consistent with most reported articles, the study also found a significant increase in contractile hyperactivity patterns and esophagogastric junction outflow obstruction (EGJOO) post-transplant. Hypercontractile behavior after transplantation does not seem

to be related with any prior motor disorder, is more common in patients with poorer outcomes, and persists over time. Interestingly, regarding the latter aspect isolated cases have been reported where contractile hyperactivity subsided and normal motility recovered within few months (6) and at 2 years post-transplant (20). Establishing the cause of esophageal hypercontractility and its potential impact on allograft dysfunction is challenging. The two mechanisms most commonly involved in the origin of this motor disorder are excessive muscle fiber excitation, which results in muscle layer hypertrophy, and esophagogastric junction obstruction. Whether this is an epiphenomenon or a determinant of transplant outcome in these patients remains to be elucidated.

EGJOO identification suggests responses to many standing questions. EGJOO at least partly explains the development of contractile hyperactivity in patients with adequate muscular responsiveness; in patients with severe hypomotility-type motor disorders (aperistalsis) its presence may originate manometry recordings similar to those of achalasia, which would explain the relatively high number of patients with this manometric diagnosis in some studies (9). Furthermore, patients with this motility pattern are more prone to develop BOS with less reflux and an increased rate of incomplete bolus transit, as detected in high-resolution impedance manometry studies, which may facilitate nonacidic microaspiration.

With these data in mind, the fact stands to reason that significant risk factors for BOS may include, in addition to GER, esophageal dysmotility, particularly EGJOO, and impaired bolus or reflux transit (16). In this regard, it is highly advisable that attempts be made to identify these factors using high-resolution impedance manometry and impedance pH-metry in order to schedule appropriate therapy, since treatment with acid secretion inhibitors or fundoplication is ineffective or even counterproductive for some patients with EGJOO.

Any efforts directed to improve the prognosis of patients with lung transplant should be considered, and further studies are needed with careful designs and enough power to better define the most appropriate therapeutic options for each individual patient.

Antonio Ruiz-de-León-San-Juan
Department of Digestive Diseases. Hospital Clínico San Carlos. Madrid, Spain

DOI: 10.17235/reed.2018.5693/2018

REFERENCES

- Almeida Fortunato G, Mota Machado M, Feijó Andrade C, et al. Prevalence of gastroesophageal reflux in lung transplant candidates with advanced lung disease. *J Bras Pneumol* 2008;34(10):772-8.
- Boehler A, Estenne M. Bronquiolitis obliterante posterior al trasplante. *Eur Respir J (edición española)* 2004;5(2):106-19.
- Pacheco-Galván A, Hart SP, Morice AH. La relación entre el reflujo gastroesofágico y las enfermedades de la vía aérea: el paradigma del reflujo a vía aérea. *Arch Bronconeumol* 2011;47(4):195-203. DOI: 10.1016/j.arbres.2011.02.001
- Ruiz de León San Juan A, Pérez de la Serna, Bueno JA, et al. Bronconeumopatía crónica y actividad motora esofágica. *Cirugía Española* 1987;41(monográfico):240-6.
- Sweet MP, Herbella FA, Leard L, et al. The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. *Ann Surg* 2006;244(4):491-7. DOI: 10.1097/01.sla.0000237757.49687.03
- Khan MQ, Nizami IY, Khan BJ, et al. Lung Transplantation Triggered "Jackhammer Esophagus": A Case Report and Review of Literature. *J Neurogastroenterol Motil* 2013;19:390-4. DOI: 10.5056/jnm.2013.19.3.390
- Basseri B, Conklin JL, Pimentel M, et al. Esophageal motor dysfunction and gastroesophageal reflux are prevalent in lung transplant candidates. *Ann Thorac Surg* 2010;90:1630-6. DOI: 10.1016/j.athoracsur.2010.06.104
- Raviv Y, D'Ovidio F, Pierre A, et al. Prevalence of gastroparesis before and after lung transplantation and its association with lung allograft outcomes. *Clin Transplant* 2012;26:133-42. DOI: 10.1111/j.1399-0012.2011.01434.x
- Akiyama J, Pasricha PJ, Weill D, et al. Esophageal Dysmotility After Lung Transplantation Assessed by High-Resolution Manometry. *Gastroenterology* 2011;140(5Suppl. 1):S-303.
- Ruiz de León San Juan A, Sevilla Mantilla C, Pérez de la Serna JA, et al. Comportamiento pH-métrico de pacientes con esofagitis erosiva grave y en enfermedad por reflujo asociada a síntomas respiratorios *Rev Esp Enferm Dig* 2004;96(Supl. I):0-21.13.
- Vaquero Barrios JM, Redel Montero J, Santos Luna F. Comorbilidades con impacto pronóstico tras el trasplante pulmonar. *Arch Bronconeumol* 2014;50(1):25-33. DOI: 10.1016/j.arbres.2013.11.010
- Castor JM, Wood RK, Muir AJ, et al. Gastroesophageal Reflux and Altered Motility in Lung Transplant Rejection. *Neurogastroenterol Motil* 2010; 22(8): 841-50. DOI: 10.1111/j.1365-2982.2010.01522.x

13. Hadjiliadis D, Duane Davis R, Steele MP, et al. Gastroesophageal reflux disease in lung transplant recipients. *Clin Transplant* 2003;17:363-8. DOI: 10.1034/j.1399-0012.2003.00060.x
14. Kobeissy AA, Saeed A, Alaradi O. Esophageal Dysmotility as a Major Causative Factor for Reflux in Lung Transplant Candidates. *Gastroenterology* 2011;140(Suppl. 1):S-256.
15. Lien D, Weinkauff J, Kapasi A, et al. Esophageal Motility and Impedance-pH in Lung Transplant Recipients. Abstracts. *The Journal of Heart and Lung Transplantation* 2014;32(4S),809,S293;S294. DOI: 10.1016/j.healun.2014.01.786
16. Tangaroonsanti A, Lee AS, Crowell MD, et al. Impaired esophageal motility and clearance post-lung transplant: risk for chronic allograft failure. *Clin Transl Gastroenterol* 2017;8(6):e102. DOI: 10.1038/ctg.2017.30
17. Fortunato GA, Machado MM, Andrade CF, et al. Prevalence of gastroesophageal reflux in lung transplant candidates with advanced lung disease. *J Bras Pneumol* 2008;34(10):772-8. DOI: 10.1590/S1806-37132008001000004
18. Ciriza-de-los-Ríos C, Canga-Rodríguez-Valcárcel F, de Pablos Gafas A, et al. Esophageal motor disorders are frequent during pre and post lung transplantation. Can they influence lung rejection? *Rev Esp Enferm Dig* 2018;110(6):344-51. DOI: 10.17235/reed.2018.5263/2017
19. Fouad YM, Katz PO, Hatlebakk JG, et al. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. *Am J Gastroenterol* 1999;94(6):1464-7. DOI: 10.1111/j.1572-0241.1999.1127_e.x
20. Aggarwal P, Bansal V, Aggarwal N, et al. The case of self-resolving type III achalasia after bilateral lung transplant. *Neurogastroenterol Motil* 2017;29:e13048. DOI: 10.1111/nmo.13048