LETTER TO THE EDITOR

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Bilateral lung transplantation in cystic fibrosis with hepatitis C infection – a study of two cases

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Cystic fibrosis (CF) is one of the most common hereditary diseases in Caucasians – it affects more than 70 000 patients worldwide [1]. Mutation in the CFTR gene leads to inappropriate synthesis of the chloride anion channel, which interferes with the regular function of multiple organs. Pulmonary-wise, CF manifests by the presence of thick, immobile secretions in the lungs, which increases the incidence of respiratory tract infections. Median survival rate for patients in the last decades has increased – over a half of the children with CF, born between 2013 and 2017, are expected to live 44 years or more [1]. The development of pharmacotherapy and a variety of remedial solutions give a high chance for longer survival of CF patients, and it is predicted that the number of effectively cured adults will continue to grow in future. However, some CF patients require a more radical life-saving solution to tackle the respiratory insufficiencies – lung transplantation (LuTx). Identification of transplant candidates is still an evolving discipline which aims to provide the best survival benefit for all of the patients qualified for this procedure [2].

In this Letter, the history of two male patients who underwent a double LuTx (1st in 2015; 2nd in 2016) after eradication of hepatitis C virus (HCV) infection will be presented. Their cases were the first of this kind in Poland. As seen in the case of patient 1, a carefully planned operation and intensive care after the procedure can lead to satisfactory therapeutic results and significant improvement of the life standard of critically ill patients. However, LuTx can also be a highly challenging procedure. As was seen in the case of patient 2, asymmetry of the native lungs, hilar fibrosis and the risk of potential HCV viral multiplication lead to repetitive exclusion of the patient from this procedure in multiple centers in Europe and United States. However, LuTx was performed with a therapeutic outcome surpassing initial predictions.

The main intention of lung transplantation was to improve the outcomes in patients suffering from end-stage lung disease. The most important indications for LuTx referral and the factors which may be further related to post-transplantation survivorship are presented in Table I.

In accordance with the International Society for Heart and Lung Transplantation [3], the main indications for LuTx referral in the presented CF patients were: forced expiratory volume in 1 s (FEV_1) below 30%, 6-minute walk test results under 400 m, development of pulmonary hypertension in the absence of a hypoxic exacerbation (patient 1), episodes of acute respiratory failure, increasing antibiotic resistance with poor clinical recovery from exacerbations and life-threatening haemoptysis (patient 1).

However, in the presented cases there were pre-transplant risk factors which gave a prognosis of poor long-term survival after LuTx – insulin-dependent diabetes mellitus (patient 1) and low BMI (patient 2).

The main reason for postponing the procedure in both cases was presence of HCV viral mRNA (which was successfully eradicated before the LuTx). At that time it was listed as one of the absolute contraindications, as it was said to significantly increase the risk of graft rejection [4].

In the case of patient 2, he first presented with hepatitis C infection in 2006, and then in 2009 he underwent interferon-α and ribavirin treatment. In 2014 laboratory results showed the HCV reactivation and the patient was treated with pegylated interferon and sofosbuvir, but the therapy had to be interrupted due to pulmonary exacerbations. Finally, in June 2015 the level of HCV-RNA was under the cut-off line and the patient was continued to be treated with ribavirin 800 mg with sofosbuvir 400 mg, and in late 2015 he underwent LuTx. Since then, he has presented no viral RNA, with follow-up blood tests in July, Au-

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Table I. Clinical presentation of patients 1 and 2

Factor	Patient 1	Patient 2
Date of LuTx	6.01.2016	30.09.2015
Age (at the LuTx)	38 years old	32 years old
Main indications for LuTx	Complete respiratory failure pulmonary hypertension recurring hemoptysis	Complete respiratory failure
BMI (on admission for LuTx)	20.05 kg/m^2	17.21 kg/m^2
Spirometry before LuTx	FEV_1 20%	FEV_1 23%
Spirometry after LuTx (from the day of discharge)	FEV_1 74%	FEV_1 49%
6MWT before LuTx	240 m	220 m
6MWT from April 2019	650 m	–
BAL grew cultures (before LuTx)	*P. aeruginosa* (two strains) *S. aureus MSSA*	*S. aureus* MRSA *Achromobacter* spp. MDR *P. mirabilis* *A. xylosoxidans* *R. ornithinolytica* *S. viridans* *Neisseria* spp.
HCV eradication (method)	12.2015 (sofosbuvir)	08.2014 (sofosbuvir + ribavirin)
Pancreatic insufficiency	Diabetes mellitus (since 2001 insulin related)	Exocrine insufficiency
Surgical circumstances	• Diabetes mellitus • Embolisation of bronchial arteries (2010) • Pulmonary hypertension	• Asymmetry and displacement of organs in the thoracic cavity (at the age of 6: lower lobectomy, resection of segments 4 and 5 of the left lung) • Bronchiectasis • Embolisation of bronchial arteries (2013)
Circulatory support	ECMO	ECC
Post-Tx complications	Acute postoperative renal failure	Reoperated – 300 ml hematoma of the left pleural cavity, pericardial tamponade
ALAD	Absent	On 9th day after LuTx
Episodes of ACR	Absent	March 2018 June 2018
CLAD	Absent	BOS
Survival	Alive, over 3 years after LuTx	Died 39 months after LuTx

LTx – lung transplantation, BMI – body mass index, 6MWT – 6-minute walk test, BAL – bronchoalveolar lavage, HCV – hepatitis C virus, ALAD – acute lung allograft dysfunction, CLAD – chronic lung allograft dysfunction, FEV_1 – forced expiratory volume in 1 second, MSSA – methicillin-sensitive Staphylococcus aureus, MRSA – methicillin-resistant *Staphylococcus aureus*, MDR – multi-drug resistant, ECMO – extracorporeal membrane oxygenation, ECC – extracorporeal circulation, BOS – bronchiolitis-obliterans-syndrome.

gust and September 2015. A standard therapeutic scheme for this drug combination should be continued between 12 and 24 weeks [5]. After a consultation with a specialist in hepatology and infectious diseases, it was decided that the treatment should extend to the full 24 weeks (it was ended in January 2016). Unfortunately in May and June 2018, the patient had two episodes of acute cellular rejection (ACR). He was treated with gamma globulin infusions and later with multiple cycles of extracorporeal photopheresis, but in November 2018, 3 years and 3 months after the LuTx, the patient died due to chronic graft dysfunction in the form of bronchial obstructive syndrome (BOS).

As for the results in patient 1, from the beginning he underwent a sofosbuvir-based therapy leading to complete eradication of HCV infection in 2014. As in the case of patient 2, this case was also consulted with a specialist in hepatology and infectious disease after which a therapeutic model of 1 × 400 mg was chosen. Multiplex real-time polymerase chain reaction (PCR) from June 2015 confirmed absence of HCV-associated viral RNA. However, in January 2016 HCV mRNA was detected, so it forced a change of immunosuppressive pharmacotherapy model from mycophenolate mofetil to azathioprine 50 mg. Throughout all this time the patient was under careful supervision of the Hepatology Department. On 6th of July 2016 a blood test for HCV mRNA was performed – it returned negative.

Overall, the undertaken therapeutic actions were risky, but ultimately proved to be right. Nowadays, HCV infection is recognized as curable, but the infection remains a relative contraindication [2]. Although CF-HCV coexistence in a potential LuTx recipient remains a clinical challenge, hepatitis C infection can be successfully eradicated before the lung transplantation and therefore should not be considered as an indication for exclusion from LuTx referral.

Disclosure

The authors report no conflict of interest.

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