Case report

Liver transplant recipient with respiratory failure due to pulmonary fibrosis related to telomere disease requiring lung transplantation

Mandeep Singh [*], Sheharyar K. Merwat, Jeffrey H. Fair, Alexander G. Duarte

Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA

A B S T R A C T

Short telomere syndrome (STS) is characterized as multiorgan dysfunction presenting with unexplained cytopenias, cryptogenic cirrhosis and pulmonary fibrosis. We present a liver transplant recipient that gradually developed hypoxic respiratory failure attributed to idiopathic pulmonary fibrosis associated telomere disease that culminated in a successful single lung transplantation.

1. Introduction

Liver transplant related respiratory complications are common in the post-operative period becoming less frequent in the subsequent months and rare one year after transplantation. We present an unusual case of an adult patient with cryptogenic cirrhosis that underwent liver transplantation and developed exertional dyspnea followed by gradual chronic hypoxic respiratory failure eventually diagnosed with pulmonary fibrosis due to shortened telomere disease. Due to progressive respiratory failure, a single lung transplant was successfully performed. This case highlights short telomere syndrome (STS) as an enigmatic multisystemic disease with blood dyscrasias, cryptogenic cirrhosis, and pulmonary fibrosis [1].

2. Case presentation

A 57-year-old man with cryptogenic cirrhosis underwent an uncomplicated liver transplant and 8 months after transplantation reported exertional dyspnea with moderate physical activities. He denied cough, fevers, or chest pain and was a former 20 pack-year smoker without a family history of lung or liver disease. Physical examination revealed room air SpO2 99%, respiratory rate 24 min^{-1}, pulse 74 min^{-1}, blood pressure 114/70 mm Hg, temperature 36.6 °C with clear lung fields and no digital clubbing. A review of chest X-ray revealed no consolidation or effusion. Laboratory data revealed normal WBC 6.7, Hgb 13.1 g/dL, plts 228 k and creatinine 0.8 g/dL. Medications included

lisinopril, tacrolimus, sirolimus, and prednisone. A review of pre-liver transplant abdominal CT demonstrated lower lobe ground glass opacities (Fig. 1A) that compared to current chest CT revealed new lingular opacities and bilateral subpleural septal thickening (Fig. 1B). Pulmonary function testing (PFT) demonstrated a restrictive ventilatory defect, without exercise induced desaturation (Table 1). Over the following months, a nonproductive cough developed along with progressive exertional dyspnea. Repeat PFT demonstrated a decline in lung function (Table 1). Additionally, six-minute walk demonstrated exercise desaturation (Table 1) and supplemental oxygen (3 L/min) was prescribed for use with physical activities. Laboratory studies demonstrated macrocytosis (Hgb 12.1 g/dL, 102 MCV fL), normal renal and liver function tests (LFT). With symptomatic worsening and lung function decline, consideration for drug induced lung disease and pulmonary infectious complications were raised and sirolimus was discontinued. Bronchoscopy revealed normal airways with minimal secretions. Analysis of bronchoalveolar lavage (BAL) demonstrated a predominance of neutrophils and cultures for bacteria, fungi, and acid-fast bacilli revealed no growth. Transbronchial lung biopsies were nondiagnostic. Follow-up chest CT (Fig. 1C) demonstrated increased subpleural reticulations with lower lobe traction bronchiectasis compared to the earlier chest CT images. Subsequently, a thoracoscopic surgical lung biopsy of the left upper and lower lobes was performed and lung histopathology confirmed a diagnosis of usual interstitial pneumonitis (Fig. 2). To understand the mechanism for the development of post-liver transplant idiopathic pulmonary fibrosis, we requested genetic testing but this was deferred

---

* Corresponding author.
E-mail address: mansingh@utmb.edu (M. Singh).

Fig. 1. Chest Imaging: A) Lung images from abdominal CT scan (prior to liver transplant) with ground glass opacities in the lower lobes; (B) Chest CT (8 months post-liver transplant) with lower lobe subpleural septal thickening, new ground-glass opacities and scattered subpleural cysts; and (C) chest CT (28 months post-liver transplant) with progressive, diffuse subpleural reticulations with traction bronchiectasis more prominent in the lower lobes.

Table 1
Pulmonary function tests, arterial blood gas and 6 min walk results.

Pulmonary function	8 months after liver transplant	16 months after liver transplant	20 months after liver transplant
FVC, L (%pred)	1.86 (41%)	1.61 (35%)	1.76 (39%)
FEV1, L (%pred)	1.65 (45%)	1.26 (35%)	1.49 (41%)
TLC, L (%pred)	3.16 (48%)	2.76 (41%)	2.56 (36%)
DLCOcor, ml/min/mmHg (%pred)	13.67 (41%)	11.6 (35%)	
FiO_2	0.21	0.21	0.21
pH	7.37	7.39	7.39
$PaCO_2$, mmHg	33	37	39
PaO_2, mmHg	94	95	68
Six Min Walk			
Distance, feet		1050	600
Exercise Oxygen Saturation		91%	84%

due to financial cost to the patient. Instead, a peripheral blood sample was obtained and flow cytometry-fluorescence in situ hybridization (Flow-FISH) assay was performed that demonstrated circulating lymphocyte and granulocyte telomere lengths less than the fifth percentile for age. This confirmed a diagnosis of telomere disease related pulmonary fibrosis and cryptogenic cirrhosis. A retrospective review of complete blood counts (CBC) before liver transplantation revealed normal white blood cell counts and macrocytic anemia with mean corpuscular volume (MCV) values that ranged from 99 to 102 fL.

Once the cause for progressive hypoxic respiratory failure was established as idiopathic pulmonary fibrosis (IPF), nintedanib was prescribed but discontinued after 2 weeks due to rising LFTs that resolved after medication discontinuation. Subsequently, a multidisciplinary group was convened to discuss lung transplantation as an option and 34 months after liver transplantation, an uncomplicated left single lung transplant was performed. The knowledge that the patient had shortened telomere syndrome (STS), allowed the lung transplantation team to avoid induction therapies with T-cell depleting agents. Eighteen months post-lung transplant, his symptoms are improved without supplemental oxygen and his liver allograft function remains normal.

3. Discussion

Telomeres are located on the end of chromosomes and consist of repetitive nucleotide sequences and protein structures that protect chromosomal ends from erosion and avoid loss of genetic material during cell division [1]. Telomere length can be assessed from circulating lymphocytes and granulocytes using commercially available assays including quantitative polymerase chain reaction (Q-PCR), quantitative fluorescence in situ hybridization (Q-FISH) and Flow-FISH. A telomere length stratified to age-matched controls less than the 10th percentile is supportive of a diagnosis of STS [1,2]. STS represents a rapid aging process arising from sporadic or genetic mutations in telomerase reverse transcriptase and telomerase RNA genes [1]. Dyskeratosis congenita is a more severe form of STS that typically presents in
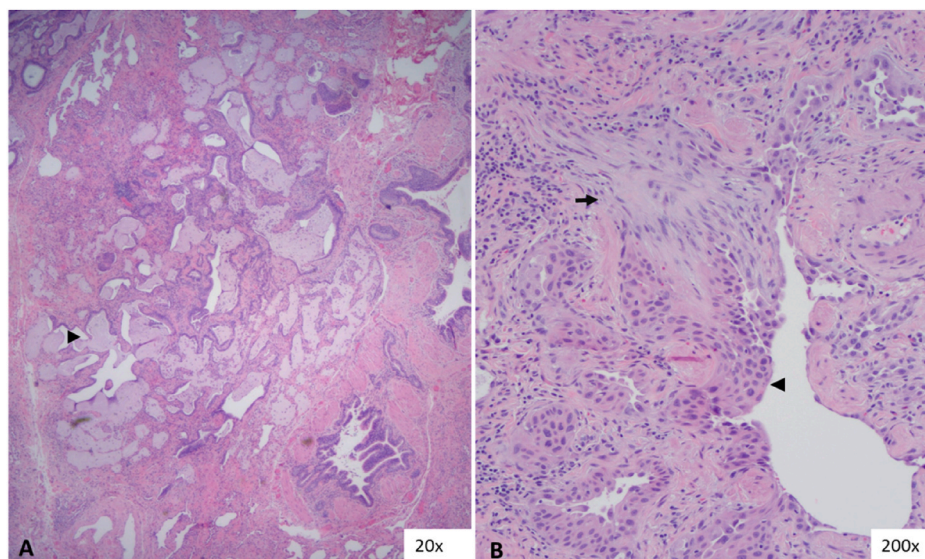

Fig. 2. Surgical lung biopsy of lower lobe. A. Advanced interstitial fibrosis with peripheral accentuation causing architectural distortion. There is mucostasis (arrowhead) associated with bronchiectasis and extension to the alveolar parenchyma (H&E, original magnification 20x). B. Fibroblastic focus (arrow) consists of fibroblasts and myofibroblasts, covered by metaplastic epithelium (arrowhead) (H&E, original magnification 200x).

the pediatric population, as a multisystem disorder including bone marrow failure, abnormal skin pigmentation, nail dystrophy, and oral leukoplakia [3]. In adults, telomere related disease is characterized by blood cell dyscrasias including anemia, macrocytosis, thrombocytopenia, cirrhosis, and idiopathic pulmonary fibrosis [1,2]. Other pulmonary manifestation of STS includes chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, combined pulmonary fibrosis and emphysema and pleuroparenchymal fibroelastosis [4]. STS should be suspected in individuals with a family history of idiopathic pulmonary fibrosis, personal or family history of premature graying of hair (before age 30), unexplained cytopenias or bone marrow failure and cirrhosis. In adults, telomere mediated disease can manifest as different phenotypes with isolated or multiorgan disease as idiopathic pulmonary fibrosis, cirrhosis and hematopoietic failure. Investigators have reported the prevalence of hepatic involvement in patients with telomere disease to be 7–40% [5,6]. In our patient, the presence of cirrhosis, IPF, and macrocytosis, led to obtaining telomere length, and established the diagnosis of STS.

Similar to the current case, a case series described adults with cirrhosis and pulmonary fibrosis associated with short telomere syndrome that underwent liver and lung transplantation. A patient underwent a liver transplant followed 12 months later by lung transplant and was noted to have mild ILD findings on chest CT and severe reduction in diffusion capacity before liver transplantation [7]. Moreover, another report described abnormal diffusion capacity in a majority of patients with telomere disease and hepatic involvement [6]. In order to better identify telomere disorders in patients with portal hypertension and cryptogenic cirrhosis, an algorithm has been proposed with emphasis on personal and family medical history, liver histology and telomere length measurements [8]. Moreover, caution should be used in interpretation of post-transplant telomere length measurements as these alone are less than ideal for the diagnosis of STS.

In patients with IPF, a diagnosis of STS can have an impact on medical management. In a post hoc analysis of the PANTHER study, patients with IPF and telomere length ≤10th percentile treated with prednisone, azathioprine and N-acetylcysteine were more likely to be hospitalized or experience an exacerbation compared to patients with IPF and telomeres >10th percentile [9]. The authors implicated the immunosuppressive regimen as the cause for the adverse events that highlights the susceptibility of this group of patients with shortened telomere length to azathioprine. Decreased survival has been observed in patients with IPF and STS such that lung transplantation is the best treatment option [4,9]. However, patients with IPF and STS are at risk for poor outcomes from complications of immunosuppressants on bone marrow and cytomegalovirus (CMV) related infections [4]. Despite normal peripheral cell counts, patients with STS may have limited bone marrow reserve and in vitro studies indicate accelerated telomere shortening can occur with exposure to antimetabolite transplant medications [4]. Consequently, to mitigate telomere shortening a change in induction immunosuppression by avoiding T cell depleting agents is preferred. As such, bone marrow failure can be heterogeneous and multidisciplinary consultation with a hematologist to assess bone marrow function is recommended [4]. Knowledge of telomere length is important as lung transplant recipients with shorter telomere length were reported to have more episodes of leukopenia requiring granulocyte colony stimulating factor and CMV viremia among CMV mismatch recipients [4,10]. In addition, patients with STS are at higher risk of malignancy, including skin cancer. This should be taken into account regarding post-transplant skin cancer prevention as pos-aconazole and isavuconazonium are preferred over voriconazole for antifungal prophylaxis due to reports that indicate voriconazole is associated with increased risk of skin cancer [4].

4. Conclusion

Assessment of progressive hypoxic respiratory failure in a liver transplant recipient involves assessment for infectious and noninfectious complications including drug induced lung disease, pleural conditions, and pulmonary fibrosis associated with telomere disease. In adults, short telomere syndrome (STS) can present as progressive organ dysfunction manifesting as cryptogenic cirrhosis and idiopathic pulmonary fibrosis. Increased awareness of this phenotype may lead to earlier identification through the use of telomere measurements that can impact pharmacologic treatment strategy and organ transplant allocation.

Declaration of competing interest

All authors above indicate no conflicts of interest.

References

[1] M. Armanios, Telomeres and age-related disease: how telomere biology informs clinical paradigms, J. Clin. Invest. 123 (3) (2013) 996–1002, https://doi.org/10.1172/JCI66370.

[2] A.A. Mangaonkar, M.M. Patnaik, Short telomere syndromes in clinical practice: bridging bench and bedside, Mayo Clin. Proc. 93 (7) (2018) 904–916, https://doi.org/10.1016/j.mayocp.2018.03.020.

[3] M. Armanios, Syndromes of telomere shortening, Annu. Rev. Genom. Hum. Genet. 10 (2009) 45–61, https://doi.org/10.1146/annurev-genom-082908-150046.

[4] A.M. Courtwright, S. El-Chemaly, Telomeres in interstitial lung disease: the short and the long of it, Ann Am Thorac Soc 16 (2) (2019) 175–181, https://doi.org/10.1513/AnnalsATS.201808-508CME.

[5] R.T. Calado, J. Brudno, P. Mehta, J.J. Kovacs, C. Wu, M.A. Zago, S.J. Chanock, T. D. Boyer, N.S. Young, Constitutional telomerase mutations are genetic risk factors for cirrhosis, Hepatology 53 (5) (2011) 1600–1607, https://doi.org/10.1002/hep.24173.

[6] D. Kapuria, G. Ben-Yakov, R. Ortolano, M.H. Cho, O. Kalchiem-Dekel, V. Takyar, S. Lingala, N. Gara, M. Tana, Y.J. Kim, D.E. Kleiner, N.S. Young, D.M. Townsley, C. Koh, T. Heller, The spectrum of hepatic involvement in patients with telomere disease, Hepatology 69 (6) (2019) 2579–2585, https://doi.org/10.1002/hep.30578.

[7] M. Lebeer, W.A. Wuyts, D. Cassiman, W. Laleman, F. Nevens, J. Pirenne, D. Monbaliu, T. Roskams, E.K. Verbeken, A.P. Neyrinck, D.E. Van Raemdonck, G. M. Verleden, R. Vos, Multiple solid organ transplantation in telomeropathy: case series and literature review, Transplantation 102 (10) (2018) 1747–1755, https://doi.org/10.1097/TP.0000000000002198.

[8] M.M. Patnaik, P.S. Kamath, D.A. Simonetto, Hepatic manifestations of telomere biology disorders, J. Hepatol. 69 (3) (2018) 736–743, https://doi.org/10.1016/j.jhep.2018.05.006.

[9] C.A. Newton, D. Zhang, J.M. Oldham, J. Kozlitina, S.F. Ma, F.J. Martinez, G. Raghu, I. Noth, C.K. Garcia, Telomere length and use of immunosuppressive medications in idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 200 (3) (2019) 336–347, https://doi.org/10.1164/rccm.201809-1646OC.

[10] A.M. Courtwright, A.M. Lamattina, M. Takahashi, A.J. Trindade, G. M. Hunninghake, I.O. Rosas, S. Agarwal, B.A. Raby, H.J. Goldberg, S. El-Chemaly, Shorter telomere length following lung transplantation is associated with clinically significant leukopenia and decreased chronic lung allograft dysfunction-free survival, ERJ Open Res 6 (2) (2020), https://doi.org/10.1183/23120541.00003-2020.