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Liver Transplantation for Decompensated Cirrhosis Secondary to Telomerase Reverse Transcriptase (TERT) Mutation

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Keywords

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Introduction:

Telomeres are DNA sequences on chromosome tips that protect against shortening during mitosis and are repaired by the enzyme telomerase. Mutations in the telomerase complex result in premature cellular senescence and can cause bone marrow failure, pulmonary fibrosis, and liver disease. Liver disease is associated with telomerase reverse transcriptase (*TERT)* and telomerase RNA component (*TERC)* mutations, typically presenting with nodular regenerative hyperplasia, though cirrhosis has been described.(1) Herein, we report a successful liver transplant (LT) for acute on chronic liver failure from telomere disease.

Case Presentation:

A 31-year old male with cryptogenic cirrhosis complicated by ascites and non-bleeding varices was referred for LT evaluation. His medical history included long-standing pancytopenia, osteoporosis with multiple vertebral compression fractures, and premature

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graying. His family history was notable for a maternal grandmother with cryptogenic cirrhosis. He had no metabolic risk factors, no excess alcohol use, and liver disease workup was negative for autoimmune disease, viral hepatitis, Wilson's disease, alpha-1-antitrypsin deficiency, and hereditary hemochromatosis. Liver biopsy showed minimally active chronic hepatitis with stage 3–4 fibrosis.

Underlying telomere disease was suspected. Telomere length, measured by Flow-FISH in peripheral leukocytes and granulocytes, was decreased (34% of age-predicted length, <1st percentile). Sequencing analysis revealed a heterozygote missense mutation (TERT gene variant c.2080G>A [p.Val694Met]) associated with reduced telomerase function. Cirrhosis secondary to telomere disease was diagnosed. Given his clinical stability, low MELD (15), and lack of suitable living donors, he was not listed. Radiographic evidence of interstitial lung disease (ILD) was noted but he had no pulmonary symptoms.

Twenty-one months later, he presented with acute decompensation with jaundice and large volume ascites. Precipitating causes including drug induced liver injury and superimposed infection were excluded. Transjugular liver biopsy showed severe cholestasis with progression to stage 4 fibrosis with dense fibrous septa and resolution of hepatitis. Severe portal hypertension (hepatic venous pressure gradient 28mmHg) was present. Although progressive ILD was anticipated, he had no oxygen requirement and did not meet criteria for lung transplant. His pancytopenia was attributed primarily to his splenomegaly, not bone marrow dysfunction. LT evaluation is summarized (Table 1).

Given progressive liver decompensation (MELD 40) without a reversible etiology, the patient was listed and underwent an uncomplicated orthotopic LT. He received solumedrol induction and in an effort to minimize bone marrow suppression, tacrolimus and low dose prednisone maintenance immunosuppression. Subsequent renal dysfunction at 6 months post-LT prompted transition to sirolimus. He received 12 months of cytomegalovirus prophylaxis based on high-risk serologies (donor positive, recipient negative) and reported impaired T-cell immunity in telomere disease. At 16 months post-LT, his liver allograft function remains normal, PFTs are stable without ILD progression, and pancytopenia has improved despite immunosuppression.

Discussion

LT has been reported in 6 patients with telomere disease (four with the indication of hepatopulmonary syndrome (HPS) two with non-cirrhotic portal hypertension, one with hepatocellular carcinoma and NAFLD, and one with compensated cirrhosis who had a simultaneous liver/lung transplant,(2–5) however, none for the primary indication of decompensated cirrhosis without HPS. The complexity of this disease with multi-organ involvement highlights the importance of multi-disciplinary discussions and planning for the unique challenges of post-LT management (Table 2). Telomere variants (independent of syndromes) have been associated with post-LT outcomes, suggesting biologic principals outlined may be more broadly applicable.(6) In conclusion, LT for decompensated cirrhosis due to telomere disease is safe and efficacious though requires unique considerations for post-LT care.

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Table 1.

Clinical phenotypes of telomere disease and assessment in our patient

System	Clinical Manifestation	Our patient
Bone marrow	• Bone marrow failure with triad of nail dystrophia, skin hyperpigmentation, and oral leukoplakia (Dyskeratosis congenita) • Increased risk of hematologic malignancies, (1–3% risk of leukemia) • Immunodeficiency (CVID), Fanconi Anemia, Aplastic Anemia	Bone Marrow Biopsy • 2000 (×2): Trilineage hypocellularity (25% and 15% cellularity), no myelodysplasia/fibrosis, negative flow cytometry • 2016: normal cellularity (60%), no myelodysplasia/fibrosis flow cytometry, JAK2 mutation, and myeloproliferative neoplasm (MPN) FISH analysis * were normal, chromosome analysis normal (46, XY) # • Appropriate reticulocyte index (4.75
Pulmonary	• Interstitial Lung Disease (ILD) Idiopathic pulmonary fibrosis (IPF), interstitial pneumonitis, Emphysema • Median age of onset: 51 years	• Reduced diffusing capacity (64%) • Bilateral ground glass opacities with pre-existing mild fibrotic interstitial lung disease, consistent with pulmonary edema, stable fibrosis • Evaluated by lung transplant team and did not meet criteria for simultaneous liver/lung transplant
Liver	• Cryptogenic cirrhosis, nodular regenerative hyperplasia • Portal hypertension, hepatopulmonary syndrome	• Cirrhosis: dense fibrous septae (stage 4) and resolution of hepatitis • Sever portal hypertension (hepatic venous pressure gradient 28 mmHg)
Bone strength	• Osteoporosis	• Multiple vertebral compression fractures
Cancer risk	• Solid Malignancies: gastrointestinal (colorectal/anal cancer, esophageal cancer), head and neck squamous cell carcinoma, skin cancer, glioma, renal cell carcinoma • Hematologic malignancies	• No malignancy identified

* MPN FISH analysis included probes specific for aberrations commonly associated with MPN: 1q+, −5/5q-, −7/7q-, +8, 13q-, 20q-, del(9q), and t(9;22).

No telomere length analysis or specific gene testing was performed on bone marrow aspirate

Table 2.

Unique considerations for telomere disease patients in the post-liver transplant period

Challenge	Management consideration	Our approach
Immunosuppression	• Increased sensitivity to CNI- induced nephrotoxicity • Increased risk of myelosuppression with antimetabolites • Reduced risk of rejection given impaired T-cell immune function	• Solumedrol induction • Early conversion to mTOR inhibitor (sirolimus) when renal dysfunction was identified (creatinine of 1.8 mg/dL despite tacrolimus trough level 3–5 ng/ml at month 6 post-LT) • Avoidance of anti-metabolites
CMV prophylaxis	• Impaired T-cell function and increased risk of primary and disseminated CMV infection that warrants extended prophylaxis • Myelosuppression (specifically neutropenia) and development of resistance may limit use of prolonged valganciclovir	• Avoid CMV-positive donor if possible • 12 months CMV prophylaxis • Use letermovir for CMV prophylaxis (higher resistance threshold and no myelosuppression) • Perform CMV-cell mediated immune assay (e.g. LPA or CMV ELISPOT) to determine if there is a need to extend prophylaxis >12 months
Pulmonary disease progression	• Risk of ILD progression • Risk of IPF development	• PFT and CT chest every 6 months
Bone marrow dysfunction progression	• Risk of bone marrow dysfunction, aplastic anemia	• CBC with reticulocyte count every 6 months • Bone marrow biopsy if cytopenia or inadequate reticulocytosis
Osteoporosis	• Increased risk of osteoporosis	• Limit prednisone dose and wean within first year • DEXA scan every 1 −2 years • Aggressive pharmacologic therapy (e.g., zoledronic acid)
Cancer risk	• Increased risk of squamous cell cancers • Increased risk of hematologic malignancy • Potentially increased risk of epithelial tumors	• Annual dermatology exam • No additional early screening performed, though could be considered
Family Considerations	• Inheritance can be autosomal dominant or recessive	• Referred for genetic counseling