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Severe hematologic complications after lung transplantation in patients with telomerase complex mutations

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thrombocytopenia;
myelodysplastic syndromes

BACKGROUND: Mutations in the telomerase complex (*TERT* and *TR*) are associated with pulmonary fibrosis and frequent hematologic manifestations. The aim of this study was to characterize the prognosis of lung transplantation in patients with *TERT* or *TR* mutations.

METHODS: Patients with documented *TERT* or *TR* mutations who received a lung transplant between 2007 and 2013 in France were identified via an exhaustive search of the lung transplantation network, one expert genetic laboratory, and the clinical research network on rare pulmonary diseases.

RESULTS: There were 9 patients (7 men) with *TERT* ($n = 6$) or *TR* ($n = 3$) mutations who received a single ($n = 8$) or a double ($n = 1$) lung transplant for pulmonary fibrosis. Median age was 50 years (range, 35–61 years) at diagnosis and 52 years (range, 37–62 years) at the time of lung transplantation. Thrombocytopenia was present in 7 patients before lung transplantation. After lung transplantation,

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6 patients developed myelodysplasia and/or bone marrow failure, directly contributing to death in 4 cases. Anemia was observed in 9 patients, and neutropenia was observed in 3 patients. The median survival after lung transplantation was 214 days (range, 59–1,709 days).

CONCLUSIONS: Patients with mutations of the telomerase complex are at high risk of severe hematologic complications after lung transplantation, in particular, bone marrow failure. Specific recommendations should be developed for appropriate guidance regarding hematologic risk assessment before transplantation and management of the post-transplantation immunosuppressive regimen.

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Idiopathic pulmonary fibrosis (IPF) is associated with a median survival time of about 3 years.[1] Lung transplantation has been shown to improve survival in selected patients.[2] The prevalence of IPF is estimated at 1 in 2,500 to 1 in 7,000, and 2% to 20% of patients with IPF have at least one first-degree relative with a fibrotic lung disease.[3,4] Genetic studies in familial forms of IPF led to the discovery of mutations within *TERT* (encoding the telomerase reverse transcriptase) and *TR* (encoding the telomerase RNA component), both of which are required for normal telomerase activity.[5] Heterozygous mutations within *TERT* or *TR* are detected in 15% to 20% of cases of familial forms of pulmonary fibrosis (PF), whereas they are very rarely detected in sporadic IPF (<3%).[5–7] In addition to PF, mutations in the telomerase complex are associated with mucocutaneous abnormalities, such as dyskeratosis congenita (abnormal skin pigmentation, nail dystrophy, oral leukoplakia), and possibly severe complications, including liver cirrhosis and bone marrow failure. Because the phenotype may be heterogeneous and the same *TERT* mutations can be associated with different phenotypes of lung disease even in the same family,[8] individual risk prediction is challenging.

We found evidence of a *TERT* mutation in a patient with PF who developed bone marrow failure after lung transplantation, triggering the present study. The largest published experience reports only 8 patients with telomerase mutations and lung transplantation from 3 different countries.[9] We reviewed the results of lung transplantation in all patients with PF associated with *TERT* or *TR* mutations in France to determine whether these patients were at risk of hematologic complications.

Methods

Patients

In this retrospective, observational, non-interventional study, all 10 French lung transplant centers were contacted to identify patients with *TERT* or *TR* mutations referred for lung transplantation during the period from 2009 to 2013; the genetics laboratory began to perform sequencing of these genes in 2009. In addition, cases were cross-identified through the only genetic laboratory in France that centrally assesses for telomerase mutations and by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P), a collaborative group dedicated to research on rare (so-called orphan) pulmonary diseases.

All patients with PF with known mutations of *TERT* or *TR* who received a lung transplant during the study period in France were included. The clinical charts of the patients were reviewed, and data were collected on a standardized and anonymous collection form. Chest computed tomography (CT) scans, biopsy specimens, and explants were systematically classified based on a multidisciplinary team discussion in each of the 4 expert centers involved in this study and classified according to the 2011 official American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association (ATS/ERS/JRS/ALAT) statement for IPF[2,10] and the revised classification of idiopathic interstitial pneumonia.[11] Hematologic manifestations including myelodysplastic syndromes were classified according to the 2008 World Health Organization classification.[12]

All patients or relatives gave signed consent for genetic analysis. The institutional review board of the Société de Pneumologie de Langue Française approved this study (CEPRO 2012-016).

Survival and patient characteristics at the time of lung transplantation were compared with a control group of patients with PF, extracted from the database of Agence de la Biomédecine, which collects data from all organ transplants in France, for the same period (2009–2013) and same centers. During the period from 2009 to 2013, 9 patients with known *TERT* or *TR* mutations included in this series and 196 patients with non-familial PF and unknown mutational status received lung transplants. Physicians in charge of lung transplantation in corresponding centers were queried for occurrence of myelodysplastic syndrome after transplant.

TERT and *TR* sequencing

Exons, intron-exon junctions, and promoters of *TERT* and *TR* were sequenced by bidirectional sequencing (primer sequences available on request) and compared with the reference sequences for *TERT* (NM_198253.2) and *TERC* (NR_001566.1).

Telomere length

The telomere length was evaluated by terminal restriction fragment assay. DNA from blood cells was extracted, digested by the Hinf1 and Rsa1 nucleases (which do not digest telomere DNA sequences), submitted to a Southern blot using a specific telomere probe, and compared the telomere length found in healthy age-matched controls.[13]

Statistical analysis

Data for continuous variables are expressed as median (range) and were compared by the Mann-Whitney *U* test. Categorical variables were expressed as counts and proportions and compared by Fisher's exact test. Survival was studied and compared with a