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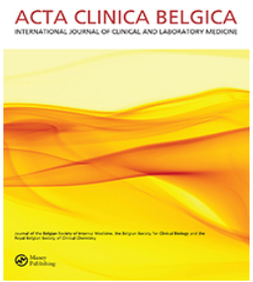

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CASE REPORT

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Telomerase-related monogenic lung fibrosis presenting with subacute onset: a case report and review of literature

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ABSTRACT

Objectives: Monogenic pulmonary fibrosis related to telomerase mutations is characterized by a large spectrum of clinical presentations. The disease may affect several organs including bone marrow, liver and skin. This case illustrates some of the most salient features of telomere-related Interstitial Lung Disease(ILD).

Methods: Single case study and review of the litterature.

Results: We report the case of a 44-year-old man admitted to our unit for subacute pulmonary fibrosis. No underlying cause could be identified. Personal and familial history was highly suggestive of monogenic telomere related lung fibrosis. Genetic investigation confirmed a mutation in the TERT gene, coding for one of the components of telomerase. Given the severe hypoxemia unresponsive to supportive treatment, he was referred for urgent lung transplantation, with a favourable outcome. Genetic counselling was proposed to his family.

Conclusions: Telomerase-related monogenic lung fibrosis may present with a subacute onset, requiring urgent lung transplantation. Extra-thoracic clinical manifestations and familial history are key elements pointing towards the diagnosis.

KEYWORDS
Idiopathic pulmonary fibrosis; telomeres; monogenic lung fibrosis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and lethal respiratory disease that affects about 3 million people worldwide [1]. Although precise mechanisms underlying the disease development remain elusive, several risk factors have been identified, including male sex, active or former smoking and exposure to occupational dust [2]. Besides, genetic factors are thought to be responsible for up to 35% of IPF development [3]. Genome-wide association studies have revealed that common polymorphisms in the promoter of MUC5B were present in more than 35% of IPF patients as compared to 9% in the general population [4]. A polymorphism in the TOLLIP gene has been associated to potential response to N-acetylcysteine treatment, although this needs to be confirmed [5]. The risk to develop an interstitial lung disease is increased when a member of the family has IPF, as about 10% of IPF patients report at least one case of ILD in their first-degree relatives [6]. In total, familial pulmonary fibrosis (FPF), defined by the occurrence of at least two cases of lung fibrosis among first-degree relatives or the occurrence of lung fibrosis below the age of 50 years, affects 2–10% of patients. Mutations in genes encoding for surfactant proteins (SFTPA1 and SFTPA2) [7,8] and for telomerase (TERT, TERC, RTEL1 and PARN) are associated with FPF; however, the causal mutation remains unidentified in more than half of the patients with suspected monogenic fibrosis [6]. Telomeres are repetitive nucleotide sequences present at the end of chromosomes, protecting them from deterioration during cell division. Mutations may effect enzymes involved in the telomerase complex, responsible for telomere production and stability. The peculiarity of telomerase mutations is their ability to affect several organs, leading to a wide variety of clinical presentation. Furthermore, telomerase-related FPF is usually more aggressive than sporadic IPF [9]. We report the case of a telomerase-related fibrosis presenting with a subacute onset requiring rapid admission to intensive care unit and referral for transplantation.

Case report

A 44-year-old man, of Turkish origins, presented at the outpatient clinic of pneumology with dyspnoea at rest which had been evolving for 2 months. Other symptoms included dry cough and a weight loss of 15 kg in 6 weeks. He had no prior medical history except a depression treated with antidepressive medication and neuroleptic drugs. He was a never-smoker. He worked as a mason and had been exposed for 10 years to stone dust and possibly asbestos. Of note, there were several cases of death from so far unidentified lung diseases in his family (Figure 1). Furthermore, one of the patient's brothers died from acute

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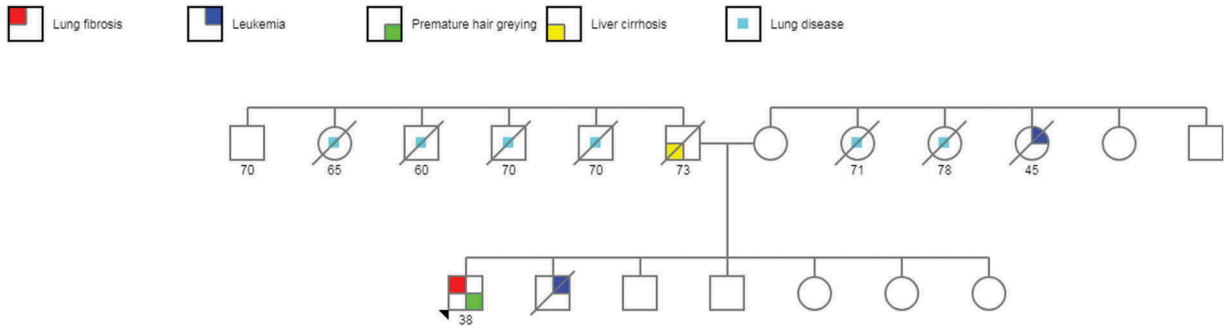

Figure 1. Family tree pedigree of the patient showing multiple relatives affected by respiratory, haematological and hepatic involvement. The anticipation phenomenon is illustrated by the younger age of disease onset of the second generation. Arrowhead represents the proband.

lymphoid leukaemia. Finally, two relatives had canitia, which is defined by early hair greying. The patient himself had grey hair since the age of 25 years. He had no fever or other sign of infection and no extra-thoracic symptoms.

On physical examination, the patient was polypneic (20 respiration per minute at rest) and desaturating (SaO_2 70%, pO2 39 mmHg without oxygen supplementation). Diffuse crackles could be heard at lung auscultation, without squeezes or wheezing. He displayed high levels of inflammation with a C-reactive protein level of 126 mg/L (normal levels <5mg/L). The initial workup revealed an underlying lung fibrosis with a high-resolution thoracic CT displaying an extensive fibrosis with ground-glass attenuation, traction bronchiectasis and enlarged lymph nodes (Figure 2). This pattern was incompatible with usual interstitial pneumonia (UIP) according to the the 2011 ATS-ERS guidelines [10] (or undetermined following the recent 2018 criteria [11]). Lung function test demonstrated a marked restrictive disease with a Forced Vital Capacity (FVC) of 20%. Other spirometric tests, especially lung diffusion capacity, were not performed due to the severe respiratory insufficiency.

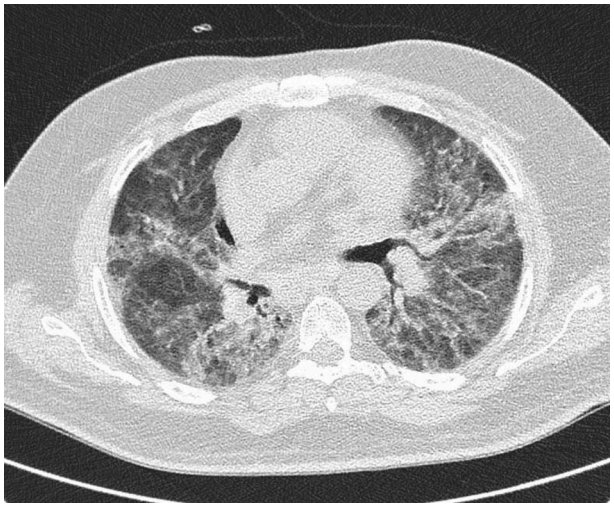

Figure 2. Thoracic CT scanner of the patient. The image is incompatible with a UIP pattern with an apical predominance and extensive ground-glass opacities.

Given his severe hypoxemia, the patient was directly admitted to a critical care unit. He received broad-spectrum antibiotics. Broncho-alveolar lavage performed by flexible bronchoscopy showed 44% neutrophils, 43% macrophages and 12% lymphocytes and failed to demonstrate any infection. Finally, in the hypothesis of an exacerbation of fibrosis, the patient received intravenous corticosteroid pulses (1000 mg per day for three days), without any improvement. Extensive workup led to the discovery of mild liver fibrosis, and the patient developed a transient thrombopenia during his stay in the intensive care unit. The origin of this feature is difficult to determine as it could be related to the adverse effects of his medication or the critical state of his illness. However, telomere syndromes are also characterized by a higher prevalence of drug-related bone marrow failure [6].

As personal and familial history pointed towards a telomerase mutation, genetic sequencing was performed and demonstrated a never-identified missense mutation of TERT (p.Gly932Ser) which was defined deleterious by the predicting software (PolyPhen-2). In light of the familial and clinical context, this variant was deemed highly susceptible of being pathogenic.

Multidisciplinary discussion with an expert centre (APHP Bichat-Claude Bernard, Paris, France) led to the decision to list the patient for lung transplantation. Due to rapidly progressive hypoxaemia, he was put on the emergency waiting list and successfully underwent bilateral sequential lung transplantation within a month.

Discussion

This case illustrates some of the salient features of telomere-related lung disease such as early onset pulmonary fibrosis, a multi-organic involvement, a familial distribution and a decreased age of onset of symptoms along with passing generations. We propose to review some of the most important features of telomere-related lung fibrosis.

Telomeres are non-coding, 9–15-kilobase-long structures found at the extremities of chromosomes which exert a protective desoxyribonucleic acid (DNA)-stabilizing role. Without telomeres, the end of chromosomes would resemble DNA double-strand breaks and would trigger DNA-repair mechanisms, potentially leading to deleterious chromosome fusions and genetic instability [12]. Without the action of the telomerase, the anti-sense DNA string would be shortened at each replication. Indeed, this ribonucleoprotein uses an RNA subunit (Telomerase RNA Component or TERC) as a template to add a DNA sequence at the end of the chromosome through its reverse transcriptase (Telomerase Reverse Transcriptase or TERT), thus preserving telomere length. A detailed description of the underlying mechanisms is beyond the scope of this article, but a complete review can be found in [13].

The regulation of telomere biology is a complex process involving several proteins, such as DKC1 [14], regulator of telomere elongation helicase 1 (RTEL1) [15], poly(A)-specific ribonuclease (PARN) [16] and the shelterin complex, composed of six different elements (Telomere repeat Binding Factor (TRF1 et TRF2), repressor/activator protein 1 (RAP1), TRF1-interacting nuclear factor 2 (TINF2), TINT1/PTOP/PIP1 (TPP1) and protection of telomeres 1 (POT1)). Mutations in one of those components lead to impaired telomere regulation, shortening of these protective structures with each mitosis and activation of protective cellular mechanisms resulting in cellular senescence or apoptosis. The relative proportions of each telomere mutations found in FPF have been recently evaluated in a large cohort by Borie et al. and telomere mutations were identified in 35% of all FPF cases. The more frequent mutations affected TERT (43%), RTEL1 (26%), TERT (14%) and PARN (11%). DKC1 and TINF2 mutations accounted both for 3% of cases (Figure 3) [6].

When present, those mutations are expressed in all cells of the organism, meaning that any organ can potentially be affected. The development of overt clinical involvement is caused by the loss of replicative potential of progenitor cell subpopulation, in particular in high turn-over tissues where replications are frequent and telomere shortening thus accelerated. Paradoxically, slow turn-over organs such as the lung are also involved in this pathology. In these organs, a second environmental hit, for example cigarette smoke or certain particles, will lead to cellular toxicity, increase in cellular turn-over, exhaustion of certain cell subpopulations and finally development of specific organ pathology. This additive effect of noxious stimuli explains the incomplete penetrance of the disease, as for example, some members of a same family will be exposed to a certain toxics while others will not. Finally, in affected families, the telomere length is transmitted vertically, meaning that each generation will have shorter telomeres than the preceding one. This will lead to a phenomenon of anticipation defined by an earlier onset of disease with each passing generation (Figure 4).

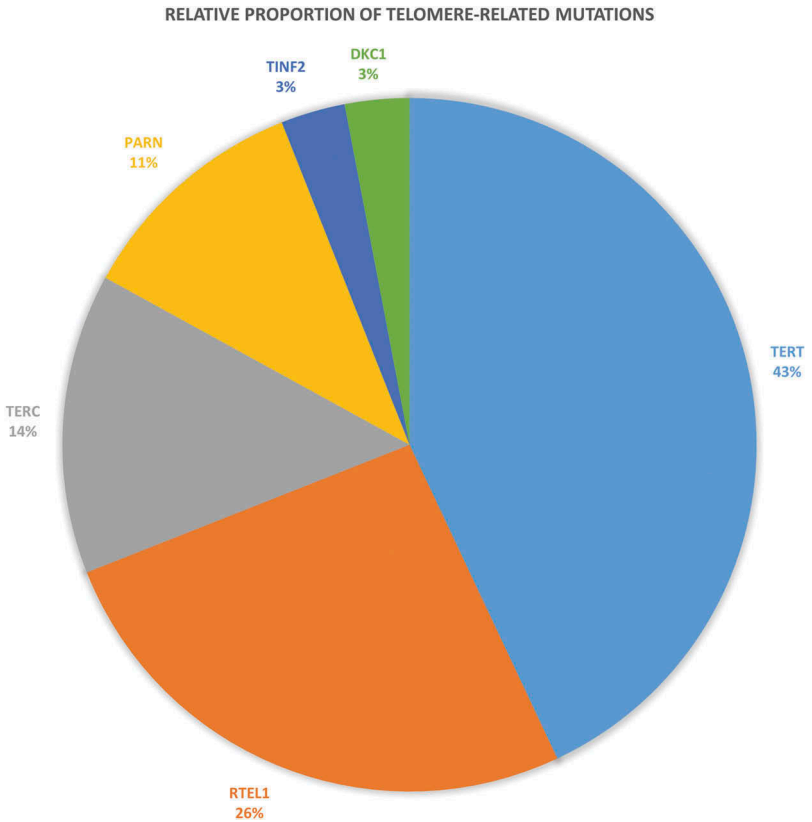

Figure 3. Relative proportion of the different telomere mutations in FPF cases where a telomere mutation was identified.

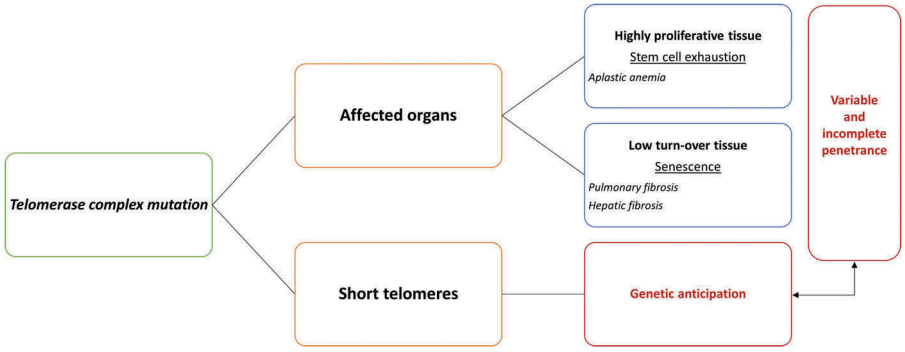

Figure 4. Illustration of the 'telomere syndrome concept'. Mutations affecting the telomerase complex lead to (a) different organ involvement and (b) transmission of short telomeres to the offspring. Those features underlie the phenomena of incomplete penetrance and genetic anticipation, respectively.

Interstitial lung disease is the most frequent manifestation of telomere-related disorders in adults [17]. Telomere-related fibrosis displays a cumulative effect of age and environmental triggers. In a cohort of TERT-mutation carriers, no patient under 40 years had developed an idiopathic interstitial pneumonia (IIP), while 50% of women and 60% of men above 60 years presented IIP-compatible features [18]. The type of mutation also seems to influence the age of onset as TERC mutation carriers are diagnosed younger than PARN-mutated patients (mean age 51 years vs. 64 years) [9]. Overall, in patients presenting with an IPF phenotype, telomere-mutated cases are diagnosed younger than in the sporadic form [19]. Additionally, a vast majority of patients report exposition to at least one pneumotoxic compound [18,20] stressing the importance of the environment.

Although a UIP pattern is encountered in 47–74% of cases on high-resolution CT scan [9,18], at least 13–20% of patients will present with an incompatible image [9,18]. In the presented case, an undetermined pattern was present, accompanied by enlarged lymph nodes. A study by Attili et al. [21] found up to 52% of non-specific lymphadenopathy in ILD. After correlation between clinical, radiological and histological data, IPF is the most common diagnosis, representing 46–86% of the cases [9,18,20]. In the remaining group, there is an important diagnostic heterogeneity, with reports of hypersensitivity pneumonitis, non-specific idiopathic pneumonia, pleuroparenchymal fibro-elastosis, unclassifiable pneumonias or desquamative interstitial pneumonitis [9,18,20]. This variable presentation is further complicated by a poor genotype–phenotype correlation, as patients affected by a same mutation can present with different types of IIPs [18]. Despite this heterogeneous presentation, pulmonary decline is consistently accelerated, with a 1.5–2-fold decrease of FVC compared to placebo arms of clinical trials [9], and mortality is uniformly distributed among the different genotypes and phenotypes.

One of the major characteristics of telomere-related lung fibrosis is the multi-organic involvements. In patients with telomere-related interstitial lung disease, haematological implication is reported in 17–50% of patients [18,20] under the form of anaemia, thrombopenia or macrocytosis [9,20]. More severe haematological diseases, such as myelodysplastic syndrome, aplastic anaemia and acute myeloid leukaemia, have also been described in this population [9,20]. Moreover, those patients are at increased risk for developing liver cirrhosis and nodular regenerative hyperplasia [6]. Additionally, dermatological involvement, mainly under the form of premature hair greying (defined as hair greying before 30 years), is present in 15–40% of patients [6].

As illustrated by this case, a genealogic history will enable the documentation of multi-organic involvement in members of the family as well as recording of an anticipation phenomenon. The combination of haematological or hepatic involvement with IIP in different family members is highly suggestive of a telomere-related disease and should prompt careful genetic evaluation. There are currently no clear guidelines regarding genetic testing and counselling of patients, and recommendations are based on expert opinions. Patients presenting at an age younger than 50 years with unexplained multi-organic involvement or premature hair greying and patients with a clear familial history of IIP should be offered genetic counselling [6]. As 10–20% of patients will have preserved telomere length [9,18], both length measurement (by Southern blot or flow-fluorescent in-situ hybridization) and mutation analysis should be performed. Importantly, only 40% of cases will have a (likely) pathogenic mutation. Testing of family members of affected patients is a matter of discussions and should be proposed after evaluation of benefit and risk.

Patients with an IPF presentation are eligible to pirfenidone and nintedanib, two anti-fibrotic agents reducing FVC decrease [22,23], although a recent study has reported a lack of efficacy of the former in this specific population [24]. Further evaluation of those treatments in this particular group is warranted in order to confirm their efficacy.

Androgens can increase telomerase activity and TERT gene expression through a mechanism which is not yet fully understood but implicates the oestrogen receptor signalling [25]. Recently, a trial with danazol, a synthetic androgen, was halted early because the primary end point, reduction in telomere attrition, was reached in all evaluable patients [26]. Although diffusion capacity was stabilized in the treated group and haematological parameters improved, this was at the cost of a high rate of side effects. Since only high-dose medication was used, complementary studies are necessary to define dosing and role of this treatment in disease treatment. Of note, low-dose danazol is currently evaluated in a clinical trial (NCT03312400).

As those patients present at a relatively young age, they are often eligible for lung transplantation. Special care should be taken regarding this subgroup, as an increase in acute and chronic kidney insufficiency [27], haematological complications (anaemia, thrombopenia) [27,28] and rare pharmacological toxicities have been reported [29]. Those effects are due to the cytotoxic nature of the administered drugs and the failing compensatory mechanisms in these mutated cases. As in dyskeratosis congenita, one of the most frequent telomeropathies, specific drug schemes could be used in order to diminish the frequency of those adverse events [30]. Although patients with telomeres <10th percentile displayed a decreased survival compared to patients with telomeres above this limit in one study [31], definitive conclusions are difficult to draw, given the scarcity of the data and the somewhat contradictory results of the published studies [28,32].

Conclusion

Patients affected by telomerase mutations-related ILD represent a complex subgroup with increased mortality and features of multi-organic involvement, transgenerational anticipation phenomenon, incomplete penetrance as well as increased drug-related adverse events. In patients in whom this condition is suspected, telomere length measurement and mutational analysis should be performed. The follow-up of these patients should be undertaken by specialized tertiary centres with experience in the multidisciplinary management that is required. Although the life expectancy is still reduced, specific treatments and adapted medication regimens should bring some improvement in the coming years.

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References

[1] Martinez FJ, Collard HR, Pardo A, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;3:17074.
[2] Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. The Lancet. 2017;389(10082):1941–1952.
[3] Evans CM, Fingerlin TE, Schwarz MI, et al. Idiopathic pulmonary fibrosis: a genetic disease that involves mucociliary dysfunction of the peripheral airways. Physiol Rev. 2016;96(4):1567–1591.
[4] Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364(16):1503–1512.
[5] Oldham JM, Ma SF, Martinez FJ, et al. TOLLIP, MUC5B, and the response to N-acetylcysteine among individuals with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015;192(12):1475–1482.
[6] Borie R, Kannengiesser C, Sicre de Fontbrune F, et al. Management of suspected monogenic lung fibrosis in a specialised centre. Eur Respir Rev. 2017;26:144.
[7] Nathan N, Giraud V, Picard C, et al. Germline SFTPA1 mutation in familial idiopathic interstitial pneumonia and lung cancer. Hum Mol Genet. 2016;25(8):1457–1467.
[8] Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009;84(1):52–59.
[9] Newton CA, Batra K, Torrealba J, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J. 2016;48(6):1710–1720.
[10] Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
[11] Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–e68.
[12] O'Sullivan RJ, Karlseder J. Telomeres: protecting chromosomes against genome instability. Nat Rev Mol Cell Biol. 2010;11(3):171–181.
[13] Armanios M, Blackburn EH. The telomere syndromes. Nat Rev Genet. 2012;13:693.
[14] Cohen SB, Graham ME, Lovrecz GO, et al. Protein composition of catalytically active human telomerase from immortal cells. Science. 2007;315(5820):1850.
[15] Vannier J-B, Sandhu S, Petalcorin MIR, et al. RTEL1 is a replisome-associated helicase that promotes telomere and genome-wide replication. Science. 2013;342(6155):239.
[16] Moon DH, Segal M, Boyraz B, et al. Poly(A)-specific ribonuclease (PARN) mediates 3'-end maturation of the telomerase RNA component. Nature Genetics. 2015;47(12):1482–1488.
[17] Armanios M. Telomerase and idiopathic pulmonary fibrosis. Mutat Res. 2012;730(1–2):52–58.

[18] Diaz de Leon A, Cronkhite JT, Katzenstein A-LA, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLOS ONE. 2010;5(5):e10680.
[19] Dressen A, Abbas AR, Cabanski C, et al. Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study. Lancet Respir Med. 2018;6(8):603–614.
[20] Borie R, Tabeze L, Thabut G, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. Eur Respir J. 2016;48(6):1721–1731.
[21] Attili AK, Kazerooni EA, Gross BH, et al. Thoracic lymph node enlargement in usual interstitial pneumonitis and nonspecific-interstitial pneumonitis: prevalence, correlation with disease activity and temporal evolution. J Thorac Imaging. 2006;21(4):288–292.
[22] King TE Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–2092.
[23] Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–2082.
[24] Justet A, Thabut G, Manali E, et al. Safety and efficacy of pirfenidone in patients carrying telomerase complex mutation. Eur Respir J. 2018.
[25] Calado RT, Yewdell WT, Wilkerson KL, et al. Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. Blood. 2009;114(11):2236–2243.
[26] Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. New England J Med. 2016;374(20):1922–1931.
[27] Tokman S, Singer JP, Devine MS, et al. Clinical outcomes of lung transplant recipients with telomerase mutations. J Heart Lung Transplant. 2015;34(10):1318–1324.
[28] Borie R, Kannengiesser C, Hirschi S, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. J Heart Lung Transplant: Official Publ Int Soc Heart Transplant. 2015;34(4):538–546.
[29] Calado RT, Regal JA, Kleiner DE, et al. A spectrum of severe familial liver disorders associate with telomerase mutations. PLOS ONE. 2009;4(11):e7926.
[30] Nelson AS, Marsh RA, Myers KC, et al. A reduced-intensity conditioning regimen for patients with dyskeratosis congenita undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplantation. 2016;22(5):884–888.
[31] Newton CA, Kozlitina J, Lines JR, et al. Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post–lung transplantation survival. J Heart Lung Transplant. 2017;36(8):845–853.
[32] Silhan LL, Shah PD, Chambers DC, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. Eur Respir J. 2014;44(1):178–187.