Pleuroparenchymal fibroelastosis associated with telomerase reverse transcriptase mutations

To the Editor:

We read with great interest the article by Newton *et al.* [1]. They found that mutations in the telomere maintenance machinery genes (telomerase reverse transcriptase (*TERT*), telomerase RNA component (*TERC*), regulator of telomere elongation helicase 1 and poly(A)-specific ribonuclease) led to variable interstitial lung disease (ILD) phenotypes that were universally progressive [1]. We were particularly interested by the evidence for the first time in the literature of a telomere-related gene mutation associated with pleuroparenchymal fibroelastosis (PPFE). PPFE represented eight out of the 77 (10.4%) cases with genetic aberrations, which is intriguing compared with the rarity of disease among ILDs. Indeed, a possible familial propensity for the development of PPFE was originally suggested by our earlier report of three affected sisters [2]. According to other published studies, a family history of ILD is observed in 17–57% of PPFE patients [3–5].

Similarly, from 2006 to 2015, 12 patients with a diagnosis of PPFE were referred to our department for further advice; of these, 10 were investigated for *TERT* and *TERC* mutations. *TERT* mutations were identified in five (50%) cases (table 1). Noticeably, a patient with a history of "pulmonary fibrosis" in his sister, chronic liver disease and unexplained cardiomyopathy, was negative for *TERT* and *TERC* but was not tested for regulator of telomere elongation helicase 1 and poly(A)-specific ribonuclease. As in the article, our study included a preponderance of females (four out of five) (age 41–63 years). Three patients had a familial background of ILD, all had a low body mass index (mean 18.8 $kg \cdot m^{-2}$), and pneumothorax or pneumomediastinum occurred in four cases. The delay between ILD and PPFE diagnosis was quite long, ranging 14–45 months. High-resolution computed tomography (HRCT) was typical of PPFE in all cases, and was pathologically confirmed in four patients (three surgical lung biopsy (SLB), one lung explant). Our patients had rapidly progressive fibrosis, with a mean decline in diffusing capacity of the lung for carbon monoxide of 6.1% per year and a decline in forced vital capacity (FVC) of 3.7% per year. At the end of follow-up, two patients were transplanted without major haematological complications and one succumbed to an acute exacerbation following video-assisted thoracoscopy performed for pleurodesis and SLB. One untreated patient is doing well and the other continues to progress under pirfenidone. Regarding the non-mutated patients, one was transplanted, two had stable pulmonary function, and two died from terminal respiratory failure. There was no difference between groups in the mean yearly decline in FVC (−3.7% in the mutated patients *versus* −2.6% in the non-mutated; p=0.4).

Our data are consistent with those of Newton *et al.* [1] and suggest the importance of searching telomere-related gene mutations in patients with PPFE even without a family history of ILD. These findings also raise pathogenic questions.

Interestingly, two patients presented Sjögren's syndrome. Autoimmune features have already been described in PPFE [4]. Data indicate that both telomerase activity and telomerase length are modified in various systemic immune-mediated diseases, including Sjögren's syndrome [8, 9]. Accelerated telomeric erosion in immune cells resulting from inflammation could lead to premature cellular senescence and increased apoptosis, responsible for a loss of control of the immune system [8]. One may hypothesise that telomerase mutation could favour autoimmune diseases like Sjögren's syndrome.

Although pleuroparenchymal changes were typical of PPFE, with an obvious predilection for upper lobes, it is remarkable that four of our patients also demonstrated a minor interstitial fibrosis in the lower

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regions at HRCT, with a pathological pattern most reminiscent of usual interstitial pneumonia (UIP) in the lower parts at SLB in three patients. In a study of 12 PPFE patients by Reddy *et al.* [4], all seven cases with multiple biopsies showed a pattern of pathological involvement in the lower lobes, which was noted upon HRCT and corresponded with UIP in three cases. Similarly, in the study by Oda *et al.* [10], nine out of 11 patients meeting radiological criteria for the diagnosis of PPFE were histologically confirmed as

TABLE 1 Characteristics of patients with pleuroparenchymal fibroelastosis (PPFE) and reverse transcriptase (*TERT*) mutations

	Case 1	Case 2	Case 3	Case 4	Case 5
Demographics					
Sex	Female	Female	Male	Female	Female
Age years	63	41	59	59	60
Smoking status	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker
Clinical features[#]					
BMI	16	20.1	22.3	18.2	17.7
Symptom duration months	7	6	6	24	36
NYHA class	2	2	1	2	1
Cough	Yes	Yes	No	Yes	Yes
Platythorax	Yes	Yes	Yes plus pectus excavatum	Yes	No
Digital clubbing	No	No	No	No	No
Associated condition	Right breast radiotherapy	Sjögren's syndrome	No	Sjögren's syndrome	No
Telomere syndrome manifestation					
Family history	No	Father with ILD	Mother and sister with ILD	Uncle and sister with ILD	No
Personal manifestation	No	Neutropenia	Thrombocytopenia and severe osteoporosis	Osteoporosis	Thrombocytopenia and macrocytosis
PFTs[#]					
TLC % pred	72	85	106	89	106
FVC % pred	71	58	103	75	97
FEV_1 % pred	71	71	100	70	100
FEV_1/FVC %	95	93	77	75	85
D_{LCO} % pred	41	51	87	80	67
6MWT					
Distance m (% pred)	420 (74)	490 (85)	540 (91)	690 (110)	595 (100)
Minimal S_{pO_2} %	93	98	90	92	95
BAL					
Total cellularity mm^3	NA	100 000	78 000	150 000	220 000
Macrophages %		82	89	84	72
Lymphocytes %		11	10	14	21
Neutrophils %		7	0	1	4
Eosinophils %		0	1	1	3
Lung specimen	Surgical lung biopsy	Surgical lung biopsy	Surgical lung biopsy	NA	Explanted lung
Pleuroparenchymal fibrosis					
Fibrosis of the visceral pleura[#]	+++	+++	+++		+++
Subpleural IAF[#]	+++	+++	+++		+++
Interstitial elastosis[#]	+++	+++	+++		+++
Sparing of parenchyma distant from pleura	Yes	Yes	Yes		No
Bronchocentric IAFE[#]	+	+	–		+++
Perilobular IAFE[#]	+	–	–		–
Coexistent pattern in lower lobes	UIP-like	UIP-like	UIP-like		PPFE
Follow-up					
Follow-up duration months	37	34	72	68	49
Change in FVC % pred[¶]	–5	–9	–20	–4	–38
Change in D_{LCO} % pred[¶]	–17	–24	–31	–2	–44
Pneumothorax or pneumomediastinum	Yes	Yes	Yes	No	Yes
Outcome	Death (AE)	Transplanted	Alive	Alive	Transplanted

Continued

TABLE 1 Continued

	Case 1	Case 2	Case 3	Case 4	Case 5
Genetic findings					
Nomenclature of the *TERT* variation at cDNA level and protein level	c.3040G>C,p.Ala1014Pro	c.2159T>C,p.Ile720Thr	c.198_207del,p.Ala67Profs*8	c.2945G>A,p.Cys982Tyr	c.2266C>T,p.Arg756Cys
Nomenclature of the *TERT* variation at gDNA level on chromosome 5 (human genome version 19)	g.1255519C>G	g.1278883A>G	g.1294898_1294907del	g.1260614C>T	g.1278776G>A
ExAC telomerase database and other reports[+]	Absence	Absence	Absence	Absence	1/121 392 alleles [1]
Prediction of the impact of the mutation by PolyPhen (Hum Var)[§]	0.999	0.932	Not applicable	0.999	0.983
Conclusion[f]	VUSD	VUSD	Path	VUSD	LikePath

BMI: body mass index; NYHA: New York Heart Association; ILD: interstitial lung disease; PFTs: pulmonary function tests; TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; BAL: bronchoalveolar lavage; NA: not available; IAF: intra-alveolar fibrosis; IAFE: IAF and elastosis; UIP: usual interstitial pneumonia; AE: acute exacerbation; ExAC: Exome Aggregation Consortium; VUSD: variant of uncertain significance possibly disease associated; Path: pathogenic; LikePath: likely pathogenic. [+]: mild; [+++]: severe; [−]: absent. [#]: at presentation; [¶]: changes between last available and baseline PFTs; [+]: presence or absence of the *TERT* variation in the ExAC database (http://exac.broadinstitute.org/), which contains exome sequencing of about 60 000 individuals, and the telomerase database (http://telomerase.asu.edu/diseases.html#tert), which presents the published mutations identified in telomere diseases; [§]: PolyPhen Tools available at http://genetics.bwh.harvard.edu/pph2/; [f]: based on American College of Medical Genetics and Genomics recommendations [6, 7].

having PPFE with UIP, including three with a family history of ILD. However, our patients and those previously reported have shown a disease presentation clearly distinct from idiopathic pulmonary fibrosis.

It is as yet unclear whether elastosis and the more common collagen fibroproliferation are distinctive pathways of chronic scarring, and whether they may reflect discrete responses to primarily different lung damages or in differently susceptible subjects. A Brazilian group has demonstrated that elastic deposition accompanies collagen deposition in the major forms of acute and chronic idiopathic interstitial pneumonias [11]. Hirota *et al.* [12] have analysed serial lung biopsies from four PPFE patients and suggested that prior interstitial inflammation or acute lung injury may be the *primum movens* of disease. Enomoto *et al.* [13] have indicated that the amount of elastic fibres is significantly reduced in the lower than in the upper lobes in PPFE as well as in UIP. Furthermore, Miele *et al.* [14] described a spontaneous pulmonary fibrosis in aged donkeys that shared similarities with human PPFE with a localised fibrosis in the uppermost and dorsal zones. In addition, PPFE features overlap with those of apical caps, the prevalence of which increases in the elderly and may be related to microscopic tears in tissue substructure caused by the weight of the lung itself [15].

Taken together, these data suggest that the extracellular matrix, when exposed to lung injury, responds as a whole with remodelling of all its components. Patients with telomere-related gene mutation may be predisposed to tractional injury to the peripheral lung [16]. During the extracellular matrix remodelling process, the differential degree of elastosis reaction and collagen fibroproliferation between the upper and lower lobes may be due to the fact that the lung zones are subjected to different mechanical strains, with upper development of PPFE and concomitant or subsequent development of UIP in the bases.

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From the authors:

We thank H. Nunes and colleagues for their interest in our study of patients with telomere-related gene mutations associated with pleuroparenchymal fibroelastosis (PPFE) [1]. Their cohort of five patients with PPFE and rare variants in telomerase reverse transcriptase (*TERT*) is similar to ours with regard to its female predominance. Here we provide additional details of our eight cases to point out additional similarities and differences between these two cohorts (table 1).

A diagnosis of PPFE was made using multidisciplinary diagnosis and histopathological examination of lung tissue in seven of the eight cases in our cohort. While changes consistent with PPFE were seen in the upper lobes of computed tomography (CT) scans in four of the six cases for which high-resolution CT scans were available, the presence of lower lobe fibrosis resembling a usual interstitial pneumonia (UIP) lesion was also noted in four cases. Similar to the findings of H. Nunes and colleagues, we often found the co-existence of PPFE with UIP-like features (fibroblastic foci, honeycombing) on pathologic evaluation. The women in our cohort also had a low body mass index (mean 20.5, range 16.8–26.7). We also noted a high incidence of either spontaneous pneumothorax or pneumomediastinum (three out of eight patients), a high proportion of never-smokers (seven out of eight), and a wide age range at diagnosis (30–66 years). There was evidence of several manifestations of short telomere syndrome, including a family history of pulmonary fibrosis, macrocytosis, anaemia, thrombocytopenia, pancytopenia, myelodysplastic syndrome or transient liver function test abnormalities in six individuals. All had evidence of interstitial lung disease progression, with seven patients dying or undergoing lung transplantation.

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TABLE 1 Characteristics of patients with pleuroparechymal fibroelastosis (PPFE) and pathogenic rare variants in telomerase reverse transcriptase (*TERT*), telomerase RNA component (*TERC*), and regulator of telomere elongation helicase 1 (*RTEL1*)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Sex	Female	Male	Female	Female	Female	Female	Female	Female
Ethnicity	Caucasian	Caucasian	Caucasian	African American	Caucasian	Caucasian	Hispanic	Caucasian
Age at diagnosis years	60	65	60	30	33	57	64	66
Smoking status	Never	Former	Never	Never	Never	Never	Never	Never
BMI	21.6	32	18.3	21.6	26.7	18.3	16.8	20.1
Pneumothorax/ pneumomediastinum	Pneumomediastinum				Pneumothorax		Pneumomediastinum	
Family history of pulmonary fibrosis	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Telomeropathy manifestations	Transient LFT elevation	Macrocytosis	Pancytopenia, MDS	Anaemia, thrombocytopenia	Macrocytosis	Anaemia, macrocytosis		Breast cancer
Gene	*RTEL1*	*RTEL1*	*TERC*	*TERT*	*TERT*	*TERT*	*TERT*	*TERT*
DNA change	c.2206_2208delGAC	c.2005C>T	r.182g>c	c.2539G>A	c.416T>G	c.1892G>A	c.2851C>T	c.430G>A
Impact on protein	p.Asp736del	p.Gln669X		p.Gly847Ser	p.Leu139Arg	pArg631Gln	p.Arg951Trp	p.Val144Met
ExAC frequency	Absent	Absent	Absent	Absent	Absent	Absent	8.29×10^{-6}	Absent
Age-adjusted LTL percentile	<1st		<1st	6–7th	<1st	<1st		
HRCT features								
Upper zone	PPFE	Reticulations		Fibrocystic changes	PPFE with reticulations	PPFE	PPFE	
Lower zone	Reticulations	Reticulations		Reticulations, honeycombing	PPFE	PPFE	Reticulations, honeycombing	
Biopsy specimen	Explant	Surgical biopsy	Explant	Explant		Explant	Surgical biopsy	Surgical biopsy
Pathologic diagnosis	PPFE	PPFE	PPFE	PPFE		PPFE	PPFE	PPFE
UIP features		Fibroblastic foci	Honeycombing	Honeycombing			Honeycombing	Honeycombing, fibroblastic foci
Outcome	Transplant	Death	Transplant	Transplant	Alive	Transplant	Death	Death

BMI: body mass index; LFT: liver function test; MDS: myelodysplastic syndrome; ExAC: Exome Aggregation Consortium; LTL: leukocyte telomere length; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

Individuals with pathogenic variants in three different telomere-related genes (*TERT*, telomerase RNA component, regulator of telomere elongation helicase 1) were included in our PPFE cohort, whereas only variants in *TERT* were described in the cohort of H. Nunes and colleagues. All variants were very rare with allele frequencies $<10^{-5}$. Telomere lengths were not measured by H. Nunes and colleagues. For those individuals in our cohort in which blood leukocytes were available, the age-adjusted leukocyte telomere lengths were all <10th percentile, with most <1st percentile. Two of the individuals in the cohort of H. Nunes and colleagues had a diagnosis of Sjogren's syndrome. While we did not find evidence of autoimmune disease in our PPFE cohort, we did have two individuals of the 115 patients with mutations in one of four different telomere-related genes that met the diagnostic criteria for scleroderma; neither of those patients had radiographic evidence of PPFE.

We agree with H. Nunes and colleagues that a diagnosis of PPFE should bring to mind a short telomere syndrome, especially if a positive family history of pulmonary fibrosis is obtained, given its relatively high prevalence (10.4%) in patients with telomere-related gene mutations. Short telomere length independently predicts worse transplant-free survival in patients with sporadic idiopathic pulmonary fibrosis [2], and the presence of a telomere-related mutation is associated with poor outcome regardless of the specific diagnosis [1]. Therefore, the decline in lung function and poor survival described by H. Nunes and colleagues may not be related to the diagnosis of PPFE, but rather due to telomere dysregulation. Further investigation is warranted to determine the aetiology of the injury and mechanisms that lead to extracellular deposition of elastin as opposed to collagen in these patients.

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