

- the management of work-related asthma. *Eur Respir J.* 2012;39:529–45. <http://dx.doi.org/10.1183/09031936.00096111>.
12. Choudat D, Villette C, Dessanges JF, Combalot MF, Fabries JF, Lockhart A, et al. Occupational asthma caused by buckwheat flour. *Rev Mal Respir.* 1997;14:319–21. PMID: 9411616.
 13. Park HS, Nahm DH. Buckwheat flour hypersensitivity: an occupational asthma in a noodle maker. *Clin Exp Allergy.* 1996;26:423–7. <http://dx.doi.org/10.1111/j.1365-2222.1996.tb00558.x>.
 14. Valdivieso R, Moneo I, Pola J, Muñoz T, Zapata C, Hinojosa M, et al. Occupational asthma and contact urticaria caused by buckwheat flour. *Ann Allergy.* 1989;63:149–52. PMID: 2475041.
 15. Heffler E, Pizzimentis, Badiu I, Guida G, Rolla G. Buckwheat allergy: an emerging clinical problem in Europe. *J Allergy Ther.* 2014;5:168. <http://dx.doi.org/10.4172/2155-6121.1000168>.

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<https://doi.org/10.1016/j.arbr.2020.02.004>

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Pulmonary Manifestation of a Primarily Mucocutaneous Hereditary Disease[☆]



Manifestación pulmonar de una enfermedad hereditaria de expresión fundamentalmente mucocutánea

Dear Editor,

Dyskeratosis congenita or Zinsser-Cole-Engman syndrome is a rare hereditary disease with multisystemic involvement. At least 12 genes related to telomere maintenance have been implicated in the pathogenesis of the disease.

In terms of clinical symptoms, nail dystrophy, reticular pigmentation, and oral leukoplakia are the most common manifestations in this disease. Pulmonary fibrosis, although it affects only 20% of patients, causes the greatest morbidity and mortality.¹

We report the case of a 49-year-old man, referred to a pulmonology outpatient clinic due to a 6-month history of dry cough. He had seasonal rhinoconjunctivitis and dust allergy and worked in a transport company in frequent contact with truck exhaust fumes. In 2000, he was diagnosed with X-linked congenital dyskeratosis by the dermatology department, with symptoms of nail dystrophy, reticular pigmentation, and oral leukoplakia (Fig. 1A). He was also being monitored by the hematology department for aplastic anemia. Karyotype analysis in peripheral blood and bone marrow was normal. Regarding family history, only one cousin on his mother's side had been diagnosed with congenital dyskeratosis. His parents were dead and his brothers had also died when they were young, cause unknown.

Lung auscultation revealed bibasal velcro crackles and resting oxygen saturation by pulse oximetry was 98%. Chest X-ray showed predominantly reticular involvement in both upper lobes and blood test results, including the autoimmunity study, were normal.

The patient showed evidence of moderate restriction and decreased carbon monoxide diffusion capacity (DLCO) in respiratory function tests (FEV₁ 71%; FVC 71%; FEV₁/FVC 60%; TLC 66%; DLCO 62%). He also had significant desaturation during the 6-minute walk test, and covered less distance than predicted, showing moderate dyspnea at the end of the test.

The study was extended with high-resolution computed tomography (HRCT) which showed diffuse parenchymal involvement, with increased volume reduction in the left hemitorax and reticular opacities with bronchiectasis and traction bronchiolectasis in both upper lobes and the lingula, consistent with fibrosing disease (Fig. 1).

Bronchoscopy was also performed with aspiration and bronchoalveolar lavage: cytology and microbiological results were negative. Given these findings, antifibrotic treatment was started with nintedanib, which was well tolerated.

Telomeres were analyzed in the Telomeropathy Detection Department of the CSIC Institute of Biomedical Research. The study showed that the patient's telomere length was below the 10th percentile compared to the healthy population of the same age. Exon sequencing of the *DKC1* gene, associated with X-DC, showed the pathogenic variant (NM.001363.4) c.203rd>G; p.H68R in exon 4 of the *DKC1* gene in homocytosis. A family genetic study was not possible, as the patient's brothers and parents had died.

A diagnosis of mild-moderate fibrosing disease (GAP 3, stage I), associated with congenital dyskeratosis with hematological and cutaneous involvement and telomere shortening, was given.

In the last 3 months, the patient presented functional progression (57% FVC and 26% DLCO) and radiological progression on HRCT, with signs of honeycombing, with multiple cysts predominantly in the upper lobes and in the left lung, and an increased pulmonary artery caliber indicating pulmonary hypertension.

Given this rapid decline, with poor response to treatment, he was referred to 3 reference centers to be evaluated for lung transplantation. All centers rejected the procedure due to the high risk, given their limited experience in this type of patients, and the poor prognosis and likelihood of post-transplantation morbidity. Palliative care was intensified, particularly for the patient's disabling dyspnea. In June 2019, he died of respiratory failure.

The true prevalence of dyskeratosis congenita is unknown. It has been estimated to affect approximately 1 in 1 million of the population. Genetic variants with different degrees of penetrance and severity and 3 types of genetic inheritance have been identified: autosomal recessive, X-linked, and autosomal dominant.²

Genes associated with congenital dyskeratosis and telomere shortening to date include *CTC1*, *ACD*, *NHP2*, *DKC1*, *PARN*, *NOP10*, *TERC*, *RTEL1*, *TINF2*, *TERT*, and *WRAP53*. The dyskerin pseudouridine synthetase 1 (*DKC1*) gene is the most common (30%) and inheri-

[☆] Please cite this article as: Guevara Velázquez V, González JM, García Arias-Salgado E, Cordovilla Pérez R, Iglesias Heras M, Hernández Mezquita MÁ, et al. Manifestación pulmonar de una enfermedad hereditaria de expresión fundamentalmente mucocutánea. *Arch Bronconeumol.* 2020;56:468–469.

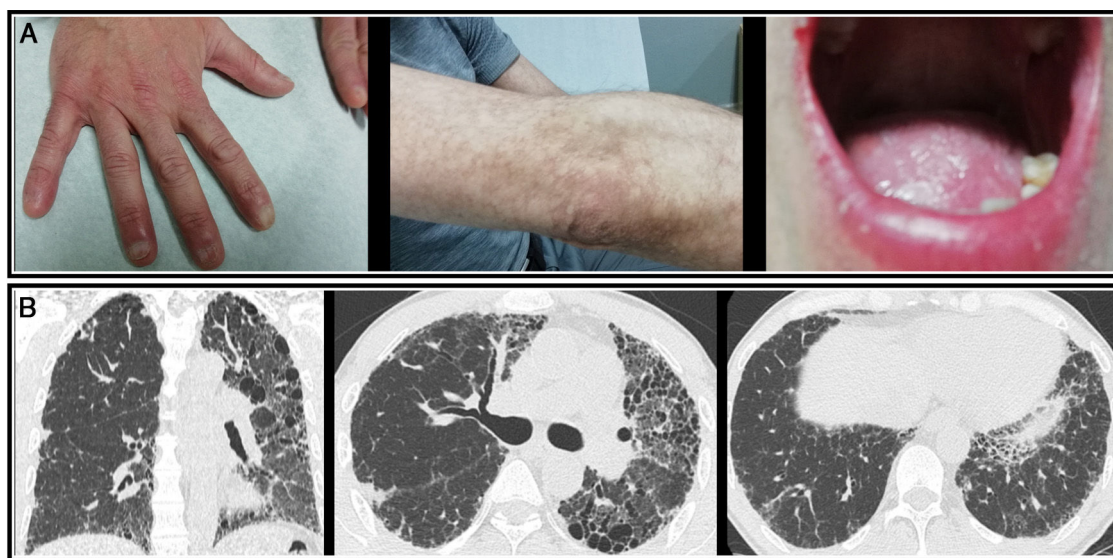


Fig. 1. (A) Mucocutaneous manifestations: nail dystrophy, reticular pigmentation, and oral leukoplakia. (B) High-resolution computed axial tomography.

tance is X-linked: about 40 pathogenic variants of this gene have been described. However, the causative gene is not identified in 20%–30% of cases.³

As observed in the clinical case presented, although mucocutaneous manifestations are the most frequent, pulmonary fibrosis constitutes one of the most serious manifestations.¹ It affects about 1 in 5 individuals with dyskeratosis congenita.⁴ It is usually diagnosed in individuals aged 20 to 40 years as a result of the study of respiratory symptoms or respiratory infection.⁵ In some cases, it develops after bone marrow transplantation. In others the cause is unknown.

The combination of pulmonary fibrosis and bone marrow failure is a powerful predictor of telomere dysfunction.⁶ Telomere shortening is described in up to 25% of cases of idiopathic pulmonary fibrosis and in more than 50% of family forms and contributes to increased epithelial apoptosis.

The mean survival of patients with associated idiopathic pulmonary fibrosis is less than 3 years from diagnosis.⁷ However, these patients mainly die due to complications from bone marrow failure (60%–70%).

The only treatment that has been shown to prolong survival in these patients is lung transplantation.⁸ However, when telomere shortening is an associated factor, prognosis is worse and post-transplant morbidity is more severe than in cases of non-familial idiopathic pulmonary fibrosis.^{9–11} Experience is scant, but cases with good outcomes have been reported in the literature and some authors believe that transplantation is a feasible option in these patients.^{2,12}

Given the rapid progress of this disease, screening for telomere shortening is a very important tool for selecting patients for referral for expeditious lung transplantation.¹³

References

1. Ballew BJ, Savage SA. Updates on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol*. 2013;6:327–37.
2. Giri N, Lee R, Faro A, Huddleston CB, White FV, Alte B, et al. Lung transplantation for pulmonary fibrosis in dyskeratosis congenita: case report and systematic literature review. *BMC Blood Disord*. 2011;11:3.

3. Savage SA. *Dyskeratosis congenita*. Seattle: University of Washington; 1993.
4. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. *Blood*. 2009;113:6549.
5. Utz JP, Ryu JH, Myers JL, Michels VV. Usual interstitial pneumonia complicating dyskeratosis congenita. *Mayo Clin Proc*. 2005;80:817–21.
6. Calado RT. Telomeres in lung diseases. *Prog Mol Biol Transl Sci*. 2014;125:173.
7. Raghun G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174:810–6.
8. Richeldi L, Collard HR, du Bois RM, Jenkins G, Kolb M, Maher TM, et al. Mapping the future for pulmonary fibrosis: report from the 17th International Colloquium on Lung and Airway Fibrosis. *Eur Respir J*. 2013;42:230–8.
9. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al. Telomere related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J*. 2016;48:1710–20.
10. Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. *Lancet Respir Med*. 2014;2:57–65.
11. Tokman S, Singer JP, Devine MS, Westall GP, Aubert JD, Tamm M, et al. Clinical outcomes of lung transplant recipients with telomerase mutations. *J Heart Lung Transplant*. 2015;34:1318–24.
12. Silhan LL, Shah PD, Chambers DC, Snyder LD, Riise GC, Wagner CL, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. *Eur Respir J*. 2014;44:178–87.
13. Courtwright AM, El-Chemaly S. Telomeres in interstitial lung disease: the short and the long of it. *Ann Am Thorac Soc*. 2019;16:175–81.

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<https://doi.org/10.1016/j.arbr.2020.02.006>

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