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Case study

Pulmonary fibrosis in dyskeratosis congenita: report of 2 cases☆

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Summary Dyskeratosis congenita (DC) is a disorder of poor telomere maintenance and is related to 1 or more mutations that involve the vertebrate telomerase RNA component. Most affected patients develop mucocutaneous manifestations and cytopenias in the peripheral blood between 5 and 15 years of age. DC patients may also develop pulmonary complications including fibrotic interstitial lung disease and pulmonary vascular abnormalities. The radiologic and pathologic features of pulmonary fibrosis associated with DC are poorly defined. Herein, we report 2 new DC cases and suggest that the radiologic and histopathologic findings may resemble usual interstitial pneumonia but may not neatly fit into the current classification of interstitial lung disease.

1. Introduction

Dyskeratosis congenita (DC) is a rare inheritable disease with shortening of telomeres due to a mutation involving several genes: *DKC1* encoding dyskerin; *hTR* for TR at the 3q region; *NOP10* and *NHP2*, components of the dyskerin complex; and *TINF2*, a shelterin component [1]. Mucocutaneous abnormalities are the most common manifestations of DC, especially nail dystrophy, abnormal skin pigmentation, and mucosal leukoplakia. Bone marrow failure and pulmonary fibrosis, however, cause more serious morbidity and account for 60% to 70% and 15% to 20% of fatalities in DC, respectively [2,3]. Fibrotic interstitial lung disease associated with DC tends to occur at much younger ages than those with pulmonary fibrosis related to heterozygous *telomerase reverse transcriptase* (*TERT*) mutations, suggesting that the genetic abnormalities in DC might cause

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more severe defects in lung repair mechanism [4]. Three main genetic variants of DC have been identified with variable penetrance and ranges of severity across individuals: autosomal recessive, X-linked, and autosomal dominant forms [3].

The cause of pulmonary interstitial fibrosis, including idiopathic pulmonary fibrosis (IPF), remains unknown. The lack of efficacy of anti-inflammatory therapy (eg, high-dose corticosteroids) in the treatment of IPF has cast doubt on the major role of chronic inflammation in the development of parenchymal fibrosis in this disease. Rather, recurrent or persistent alveolar epithelial injury with dysregulated repair is currently thought to be the major mechanism leading to progressive pulmonary fibrosis in IPF [5]. The defective telomere maintenance with impaired cell regeneration in DC patients might lead to pulmonary fibrosis as in a subset of IPF. Herein, we report clinical, radiologic, and pathologic findings of pulmonary fibrosis in 2 DC cases that underwent surgical lung biopsies.

2. Report of cases

2.1. Case 1

A 24-year-old man presented with persistent cough, dyspnea, and fever. He had a history of developmental delay including short height and learning disabilities requiring special education classes throughout elementary and high school. He also had a long history of polysubstance abuse including alcohol, tobacco, methamphetamine, marijuana, and cocaine. A chest computed tomographic (CT) scan at presentation demonstrated diffuse interstitial infiltrates. He was found to have a macrocytic anemia (hemoglobin level, 12.4 g/dL), absolute leukopenia (white blood count, 2.8×10^9/L) including neutropenia (1.3×10^9/L) and thrombocytopenia (59×10^9/L). A differential count from peripheral blood revealed increased eosinophils at 15% and monocytes at 12%. The patient was counseled on the potential role of inhalation drug abuse and smoking as inducers of the lung disease and encouraged to cease drug and nicotine use. He complied with these recommendations but, upon follow-up, demonstrated persistent restriction on pulmonary function testing with a significant reduction in his diffusing capacity at 42% of predicted. He also remained pancytopenic and underwent a bone marrow biopsy, which revealed a hypocellular bone marrow (approximately 40%) with a moderate decrease in neutrophils and megakaryocytes accompanied by a slight decrease in erythroid precursors. There was no evidence of a neoplastic process in the bone marrow.

The patient then was lost to follow-up for 3 years and presented subsequently to an urgent care center with cough and dyspnea. A chest CT showed interval progression of mid- and upper lobe–predominant peripheral interstitial opacities consistent with a fibrotic interstitial pulmonary process (Fig. 1). There was also prominent interlobular septal thickening throughout the lungs. The overall radiologic pattern was atypical for radiologic usual interstitial pneumonia (UIP), and therefore, a video-assisted thoracoscopic lung biopsy was performed from the left lower lobe. Sections demonstrated scattered fibroblast foci in a background of more chronic interstitial fibrosis showing subpleural and paraseptal accentuation, suggestive of a histologic UIP pattern (Fig. 2). However, in addition, in some areas, there was prominent lymphatic proliferation in the fibrotic interlobular septa and in the bronchovascular sheaths, superficially resembling the rare condition known as pulmonary lymphangiomatosis (Fig. 2). No honeycomb change or traction bronchiectasis was seen in this biopsy obtained from the left lower lobe, which might have been the result of sampling because the patient's reticular opacities were more prominent in the upper lungs on the chest CT scan. Elastic stains (Verhoeff–Van Gieson) were performed in addition to routine hematoxylin and eosin–stained sections, but these did not show features characteristic of pleuroparenchymal fibroelastosis. Overall findings are summarized in the Table along with previously reported cases in the literature.

This constellation of clinical and laboratory findings, including developmental delay, bone marrow failure, and pulmonary fibrosis, suggested the diagnosis of DC and triggered a medical genetics evaluation. In addition, on a more detailed physical examination, he was found to have lacy reticular hyperpigmentation of the skin around the neck and back, areas of alopecia on his scalp, slight leukoplakia of the tongue, nail dystrophy, clubbing of all 10 digits, and hypoplastic testes. A chromosomal analysis revealed a normal male karyotype. A telomere length measurement was performed on peripheral blood cells for further evaluation of DC and showed shortened telomere lengths in all leukocyte cell lines tested. Sequencing of the *DKC1* gene associated with the X-linked recessive form of DC revealed the patient to be homozygous for a sequence variant denoted c.189T>G (p.Asn63Lys).

2.2. Case 2

A 46-year-old woman presented with chest discomfort and exertional dyspnea that was first noticed while hiking in the mountains. She was an ex-smoker with a 10-pack-year smoking history. The patient had been active and physically fit until her initial presentation. Her cardiac workup was negative, but a chest radiograph revealed mild interstitial densities. She remained fairly active for the 4 ensuing years until she developed a flu-like illness with a persistent cough, sputum production, and more significant dyspnea unresponsive to antibiotics, bronchodilators or nebulizers. Three months later, a chest radiograph showed peripheral patchy interstitial changes with volume loss, and a chest CT demonstrated the presence of pulmonary fibrosis and traction bronchiectasis consistent with radiologic UIP (Fig. 3). Her