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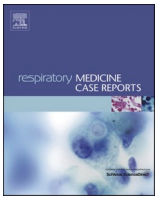

Case Report

Dyskeratosis congenita with heterozygous *RTEL1* mutations presenting with fibrotic hypersensitivity pneumonitis

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ABSTRACT

Dyskeratosis congenita is a rare genetic disorder of telomere insufficiency characterized by a mucocutaneous triad of nail dystrophy, abnormal skin pigmentation, and mucosal leukoplakia. Early diagnosis is important for multidisciplinary approach to its complications including bone marrow failure, malignancy, interstitial lung disease, and liver disease which cause significant morbidity and mortality. We report a genetically confirmed case of dyskeratosis congenita who presented with fibrotic hypersensitivity pneumonitis, highlighting non-mucocutaneous features of dyskeratosis congenita and the need to consider genetic predisposition in a patient with interstitial lung disease and combined unusual manifestations.

1. Introduction

Dyskeratosis congenita (DC) is a rare genetic disease of defective telomere regulation showing marked clinical and genetic heterogeneity. The classic form is characterized by a mucocutaneous triad of nail dystrophy, abnormal skin pigmentation, and mucosal leukoplakia. However, DC can affect multiple systems resulting in bone marrow failure (BMF), interstitial lung disease (ILD), liver cirrhosis (LC), and malignancy. Patients with single organ involvement like idiopathic pulmonary fibrosis without overt mucocutaneous symptoms may have been undiagnosed. In previous studies, up to 15% of familial and 3% of sporadic pulmonary fibrosis are associated with mutations in *TERC* or *TERT*, resulting in short telomeres [1]. Most of DC-related ILDs showed radiologic and pathologic usual interstitial pneumonia (UIP) pattern [2]. Herein we describe the sporadic case who presented with fibrotic hypersensitivity pneumonitis (HP) and was eventually confirmed with DC.

2. Case presentation

A 39-year-old male visited our pulmonology department with dyspnea and dry cough lasting more than 6 months. A medical checkup 2 years prior had revealed pancytopenia, but bone marrow biopsy did not indicate hematologic disease. The patient did not make more visits for pancytopenia. Computed tomography (CT) revealed cirrhotic liver but serologic tests for hepatitis virus were all negative. He had drunk alcohol occasionally for 10 years and quit it after the event. He was a former smoker with a 5 pack-years history and had never been exposed to occupational noxious gas or dust. He had been exposed to mold in his old house for 10 years. He had a

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family history of esophageal cancer but no other family history including pulmonary or liver disease. Inspiratory crackles were confirmed in both basal lung fields on auscultation. He had mild whitish plaque on the tongue, and mild dystrophy was observed on his finger and toe nails which had not been recognized by himself (Fig. 1).

Laboratory tests demonstrated a white blood cell count of 3600/μL, a hemoglobin of 11.3 g/dL with mean corpuscular volume of 101fl, and a platelet count of 36,000/μL. Prothrombin time was 12.4 sec, serum albumin was 3.1 g/dL, and the total bilirubin was 1.0 mg/dL. He had no ascites and encephalopathy (Child–Pugh score: 6). Arterial oxygen tension (PaO_2) was decreased to 78.6 mmHg in arterial blood gas analysis at room air. Anti-nuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-neutrophil cytoplasmic antibodies were all negative. On pulmonary function test, forced vital capacity (FVC) was 3.63 L (71% of predicted value), forced expiratory volume 1 second was 3.02 L (71% of predicted value), and diffusing capacity of the lung for carbon monoxide (DLCO) was 11.6 ml/min/mmHg (39% of the predicted value).

High-resolution computed tomography (HRCT) revealed subpleural diffuse reticular opacities with mild traction bronchiolectasis and mild basal predominance (Fig. 2).

In bronchoalveolar lavage (BAL) fluid, a total WBC count was 354/μL, with macrophages of 67%, lymphocytes of 27%, neutrophils of 2%, and eosinophils of 3%. Video-assisted thoracoscopic surgery for lung biopsy was done. Pathologic findings showed patchy, subpleural fibrosis and centrilobular cellular infiltration with fibroblastic foci, suggesting fibrotic HP (Fig. 3).

Radiological findings were indeterminate for HP, but the pathological findings were consistent with probable HP according to an official ATS/JRS/ALAT clinical practice guideline [3]. We diagnosed him with fibrotic HP based on his history of mold exposure, BAL fluid analysis, and radiologic-pathologic findings.

Due to his presentation of pancytopenia, LC, and ILD at a relatively young age, we performed genetic testing for ILD predisposition despite no remarkable family history. Whole-genome sequencing revealed heterozygosity for the stop-gain variant, c.2920C > T (p.Arg974Ter) of the *RTEL1* gene. Considering his unusual dysplastic nails and oral whitish plaque, we reached a final diagnosis of DC. The patient was treated first with steroids and mycophenolate mofetil to reduce inflammation of HP. His symptoms are being well controlled and FVC has been maintained around 70% of predicted value for one year, but an extent of interstitial fibrosis on HRCT has been increased on the 1-year follow-up HRCT. Therefore, he started on antifibrotic therapy. He is currently maintaining low dose steroid with pirfenidone and being followed up for complications of DC including pancytopenia and LC on an outpatient basis.

3. Discussion

DC is a genetic disorder associated with telomere dysfunction. Although initial descriptions of DC focused on mucocutanoues manifestations, it shows heterogeneous clinical manifestations. The skin pigmentation and nail changes usually manifest first by the age of 10 years. Almost 90% of patients have cytopenia of one or more lineages, which usually develops before the age of 20 years. BMF is a leading cause of death, and approximately 80% of patients die from infection, hemorrhage, or complications of bone marrow transplantation [4]. Hepatic involvements including LC occur in 10% of patients. Pulmonary complications, including pulmonary fibrosis and pulmonary vascular abnormalities, are observed in approximately 20% of patients. Although mucocutaneous symptoms of our case were too mild to be recognized by himself, combined manifestations of pancytopenia, LC, and ILD at a relatively young age became clues to diagnosis.

DC is also genetically heterogeneous and can be inherited in X-linked, autosomal dominant, or autosomal recessive patterns. The first gene discovered was X-linked *DKC1,* which encodes dyskerin involved in telomere maintenance and ribosomal biogenesis [4]. The *RTEL1* gene, the mutation of which presented in our case, encodes DNA-helicase involved in DNA replication, genome stability, and telomere maintenance. Heterozygous *RTEL1* mutations are observed in 5–9% of familial pulmonary fibrosis and they showed

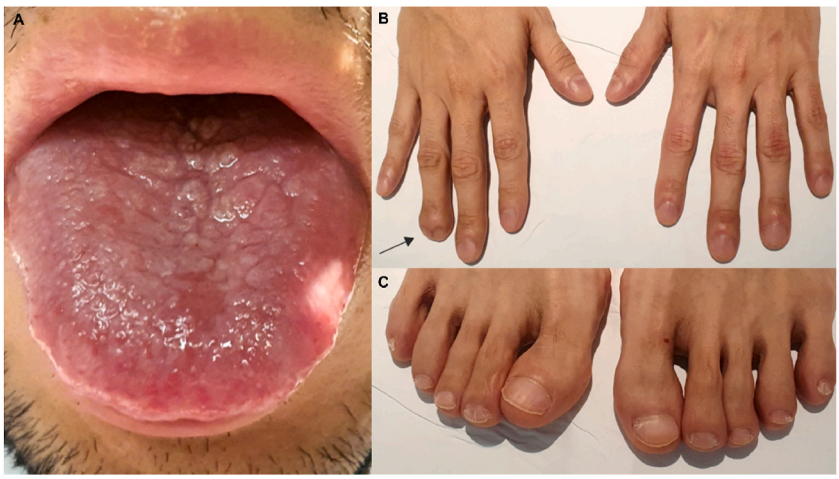

Fig. 1. Clinical photographs of the case.
(A) Multiple whitish plaques on the tongue. (B, C) Mild clubbing and nail dystrophy including longitudinal ridging, loss of nail (closed arrow), and koilonychias.

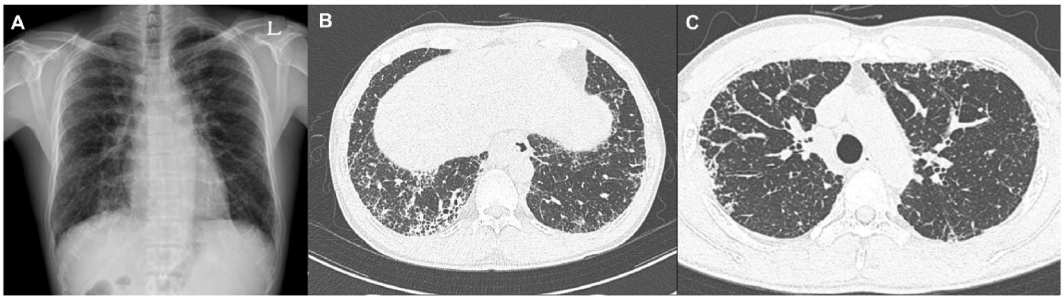

Fig. 2. Radiologic findings of the case.
(A, B, C) Chest X-ray and CT showed diffuse reticular opacity in subpleural area of both lungs without honeycombing.

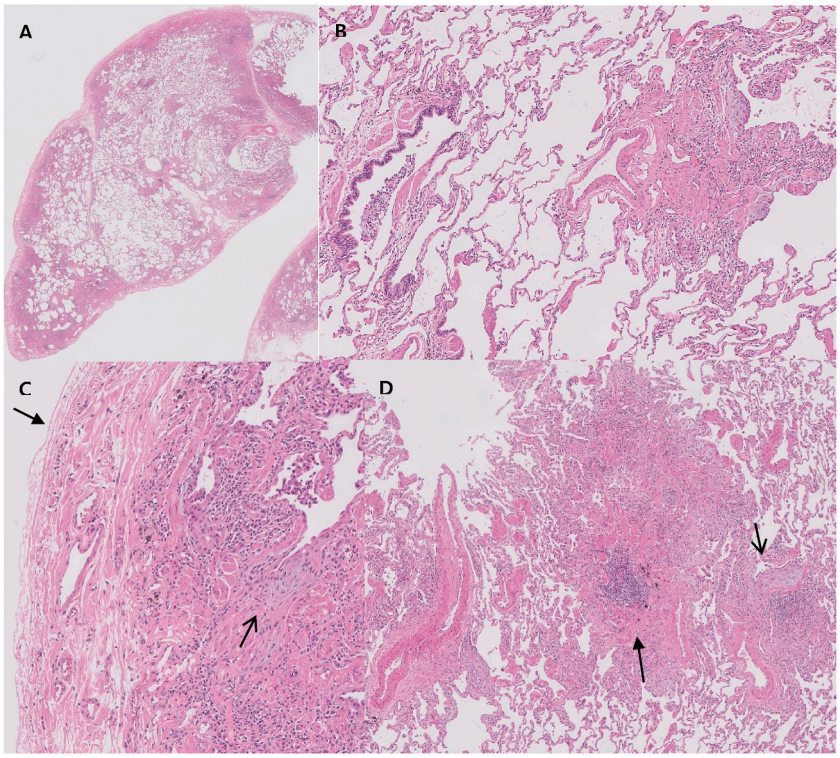

Fig. 3. Pathologic findings of the case.
(A, B) Low power field image (magnification x 10) shows peripheral dominant fibrosis and high power field image (magnification x 100) shows focal centrilobular fibrosis. (haematoxylin and eosin stain (HE) stain, (C) In the periphery of lung, old mature fibrosis (closed arrow) and fibroblastic foci (open arrow) coexist suggesting temporal heterogeneity of fibrosis (HE stain, magnification x 100) (D) At the respiratory bronchiole level, cellular infiltration (closed arrow) and fibroblastic proliferation (open arrow) show centrilobular subacute lung injury. (HE stain, magnification x 100).

heterogeneous phenotypes. Extrapulmonary manifestations including hematologic and liver disease were less accompanied compared to other telomeropathy associated ILD patients [5]. There is a hypothesis that heterozygous *RTEL1* mutation causes either mild or asymptomatic DC like our case, whereas homozygous mutation causes complete loss of telomere-regulatory function, leading to severe form like Hoyeraal Hreidarsson syndrome [6].

The previous systematic analysis revealed that ILDs associated with *RTEL1* mutation usually presented in a UIP pattern (82.6%), and the most frequent diagnosis was idiopathic pulmonary fibrosis (72.2%) [5]. However, other ILDs including fibrotic HP, connective tissue disease-associated ILD, and unclassifiable ILD were also diagnosed in patient with heterozygous *RTEL1* mutation. Although HP is an ILD related to environmental exposure, a genetic predisposition is suspected since not all individuals exposed to causative antigens develop the disease. In a previous research, next-generation sequencing identified variants in telomere-related genes such as *TERT, TERC, and RTEL1* in some patients with fibrotic HP, which were associated with worse clinical outcomes [7]. Therefore, telomeropathy such as DC may increase the genetic susceptibility to HP and leads to worse prognosis.

A standard treatment for HP is antigen avoidance and anti-inflammatory therapy including corticosteroid. However there is a lack

of evidence of therapeutic effects of corticosteroid in fibrotic HP. In the previous retrospective cohort study, corticosteroid treatment improved FVC and DLCO in non-fibrotic HP, but showed no therapeutic effect in fibrotic HP [8]. Another study demonstrated that corticosteroids had survival benefits and inhibited fibrotic progression in patients with fibrotic HP without extensive fibrosis [9]. Current strategy is to consider presence of inflammatory features before trying corticosteroid or immunosuppressants in fibrotic HP [10]. Antifibrotic therapy which may inhibit progression of fibrosis is also expected to be effective in HP with fibrosis. Several trials are assessing efficacy and safety of antifibrotic drugs including pirfenidone and nintedanib in fibrotic HP and it has been shown to reduce FVC decline with tolerable adverse effects [11–13]. Also, antifibrotic drugs reduced FVC decline safely in IPF patients carrying telomere-related gene mutation [14]. As telomeropathy is associated with relentless progression of fibrosis and worse clinical outcome not only in patients with IPF, but also in non-IPF ILDs including HP [15,16], antifibrotic therapy might be considered in patients with telomere related gene mutation presenting with fibrotic HP like our case, but further assessment is needed.

4. Conclusion

We experienced the case of dyskeratosis congenita presenting with fibrotic hypersensitivity pneumonitis without overt mucocutaneous symptoms. However, unusual combined manifestations including cryptogenic LC and pancytopenia led to the final diagnosis of DC and the patient are now being followed up for other possible complications. The case highlights the importance of considering genetic predisposition such as telomeropathy in ILD patients with unusual extrapulmonary manifestations including liver cirrhosis and pancytopenia as in our case, even in ILDs other than the UIP pattern on CT and histopathology.

Consent statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author contributions

Jin Woo Song: Conceptualization, Data curation, Investigation, Writing- Reviewing and Editing. Jinhee Han: Data curation, Investigation, Writing- Original Draft, Writing – Reviewing and Editing.

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Declarations of competing interest

All authors have no potential conflicts of interest.

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