CASE REPORT

Fatal Acute Exacerbation of Familial Interstitial Pneumonia Complicated with Dyskeratosis Congenita after Influenza Virus B Infection

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Abstract:
Dyskeratosis congenita (DC) is occasionally complicated in patients with familial interstitial pneumonia (FIP). However, there have been no reports of FIP patients with DC that develop acute exacerbation (AE). We herein report a FIP patient with DC that showed AE of FIP after influenza virus B infection. Although DC is a rare disease in clinical practice, physicians should keep in mind that FIP combined with DC has the potential to cause AE.

Key words: familial interstitial pneumonia, acute exacerbation, dyskeratosis congenita


Introduction

The prevalence of familial interstitial pneumonia (FIP) in patients with idiopathic interstitial pneumonia (IIP) is 0.5%-10% in some studies (1, 2). A previous study reported that 3.3%-3.7% of IPF patients showed FIP (3), and 20% of IPF patients were also reported to have a positive family history (4). In addition, several causative gene mutations of FIP has been reported to range widely (1%-15%) (5-7). Mutations in the genes encoding telomerase, such as telomerase reverse transcriptase (TERT)/telomerase RNA component (TERC), which is important for maintaining telomerase activity and telomere length, can cause pulmonary fibrosis.

Dyskeratosis congenita (DC) is a rare hereditary condition of ectodermal dysplasia characterized by a mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leukoplakia (8). Mutations in TERC/TERT that shorten the telomere length can cause DC. Although some DC cases combined with interstitial pneumonia (IP) have been reported (9-12), information on the clinical course of these patients is insufficient.

We herein report a case of FIP with DC that showed acute exacerbation of IP after influenza virus B infection, with a review of the relevant literature.

Case Report

A 36-year-old Japanese man with a high-grade fever, productive cough and progressive dyspnea since a few days earlier visited an internal medicine clinic. A nasal swab was positive for influenza B antigen, and he was treated with peramivir (600 mg/day). The next day, he developed pneumonia with severe acute respiratory failure (SpO₂ 70%, room air, supine) and was therefore transferred to our hospital.

He was a current smoker (20 pack-years) without any exposure to toxic materials, history of close contact with birds or a medical history of allergy or autoimmunity. He had been found to have chest X-ray abnormalities at routine health checkups three years earlier but had not undergone any further examinations. His mother, sister and uncle all...
had IP. His mother regularly visited the department of respiratory medicine in our hospital for IP. She also showed abnormal skin pigmentation on her anterior chest and evidence of bone marrow failure (e.g. anemia and thrombocytopenia). She was treated with prednisolone and pirenidone for IP. His sister was also treated for IP in another hospital but suddenly died of an unknown cause. His uncle had also been diagnosed with IP at another hospital; however, the details of the diagnosis are unknown.

On admission, he was awake and alert. His body temperature was 38.0°C, blood pressure 134/72 mmHg, SpO2 92% (O2 15 L/ min, reservoir mask), respiratory rate 28/min, and pulse rate 69 beats/min (regular). Fine crackles were audible in the bilateral lower lung fields on a physical examination. His skin showed abnormal reticulate hyperpigmentation on anterior chest imaging, and nail dystrophy was also recognized (Fig. 1), but oral leukoplakia was not apparent. The onset of nail dystrophy and skin hyperpigmentation was obscure. The neurologic examination findings were normal.

Laboratory findings on admission were as follows: white blood cell count 6,000/mm³ (neutrophils 72%, lymphocytes 19%, monocytes 6%, eosinophils 3%), hemoglobin 14.5 g/dL, platelets 8.4×10⁹/L, lactate dehydrogenase 348 IU/L, serum C-reactive protein 0.39 mg/dL, and serum Krebs von den Lungen-6 1,183 U/mL. Serum rheumatoid factor was negative, and the levels of several antinuclear antibodies and immunoglobulins were all normal. An arterial blood gas analysis (reservoir mask 15 L/min.) showed severe hypoxemia with hypocapnia (pH 7.490, PaO2 57.0 Torr, and PaCO2 24.9 Torr). Chest radiography and high-resolution computed tomography (HRCT) demonstrated bilateral diffuse ground-glass attenuations and consolidations (Fig. 2). Sputum and blood culture showed no evidence of bacterial infection. Echocardiography revealed no findings of left or right heart failure. Multiple rapid influenza antigen tests using a nasal swab were negative. We suspected DC because he had reticulate hyperpigmentation, nail dystrophy, thrombocytopenia and a family history of IP. We therefore obtained informed consent to perform a genetic test from the patient and his mother before they died.

After admission, intratracheal intubation was performed and mechanical ventilation was started, and combined treatment with peramivir, high-dose intravenous corticosteroids (methylprednisolone 1 g/day for 3 days) and immunosuppressants (cyclophosphamide and cyclosporin A) was started for acute exacerbation of FIP. Despite these treatments, his PaO2/FiO2 ratio gradually decreased, and he died on the 45th day after admission (Fig. 3). Genetic testing for known FIP and genes related to DC revealed that this patient and his mother had a point mutation in one allele of TER (73 G>C) (Fig. 4), although their telomere length had not been shortened.

**Discussion**

Our patient had FIP with DC and showed refractory acute exacerbation of his IP after influenza virus B infection. Although several reports of the acute exacerbation of FIP and a case report of acute exacerbation of IP in a patient with DC without a family history of IP have been published (13), to our knowledge, this is the first case of FIP in a patient with DC who developed fatal acute exacerbation of IP. Some cases of FIP are occasionally complicated with DC, and in addition to clinical findings, genetic testing for these conditions is useful for making a definitive diagnosis of FIP complicated with DC.

The diagnosis of FIP is usually made when there are two or more biological family members with IIP (14). Some recent genetic studies in patients with FIP have revealed the involvement of genes related to telomere and surfactant proteins in the pathogenesis of FIP (15-17). In particular, a few abnormal telomere-related genes are recognized to represent pathogenically important gene abnormalities not only for FIP and sporadic IP but also for DC, which manifests in the form of multiple organ disorders.

DC is a rare disease with a prevalence of 1 per 1 million and is a genetic illness characterized by the diagnostic triad of nail dystrophy, oral leukoplakia and skin hyperpigmentation (8). The majority of patients with DC are normally born without any symptoms or physical abnormal findings, but abnormal skin and mucus findings are seen during infancy, and multi-organ disorders, such as bone-marrow failure, are also seen in the clinical course. Clinical features in patients with DC appear before 30 years of age (18), but some patients with DC in apparent clinical symptoms may go undiagnosed. Mutations of telomere-associated genes, such as TER and TERT, have been reported in patients with DC, and a shortened telomere length is frequently seen, although some patients show a normal telomere length, as seen in the present patient (19). In addition, an association of TERC/TERT mutations with a reduced transplant-free survival in patients with pulmonary fibrosis was recently reported (20). Therefore, in patients suspected of having DC with IP based on their characteristic physical findings, a suppressed bone-marrow function and familial history, the telomere length and related genetic tests should be assessed.
as in the present patient. Given the wide ranged phenotypes of telomere-associated gene mutations, the clinical courses of FIP patients with DC may vary widely.

There have been few previous reports describing the clinical course of DC patients with IP, although DC associated with the presence of IP accounts for approximately 20% of DC cases (21). This low rate of reporting can be attributed to the condition being overlooked when the characteristic physical findings are poor (e.g. oral leukoplakia, skin hyperpigmentation and nail dystrophy). For this reason, there have been no reports of a fatal outcome in DC patients who developed acute exacerbation of IP after influenza infection. In patients with FIP, the possibility of DC also needs to be considered. Many DC patients complicated with IP are diagnosed in their 20s to 40s due to respiratory symptoms, such as dry cough, and their HRCT findings often show a radiological pattern of usual IP (10). External factors, such as smoking, and environmental factors, such as inhalation exposure to toxic materials, may affect DC patients with IP, suggesting that composite elements, including shortening of the telomere length and epigenetic DNA repair, in addition to gene mutations might be involved in the pathology of IP associated with DC (22).

Since no radical treatments for DC have been established, most treatments primarily address its complications. Lung transplantation is generally considered for DC patients with progressive IP who have respiratory failure. The roles of anti-fibrotic drugs for the chronic phase of IP and high-dose corticosteroids for acute exacerbation of IP in patients with DC remain unclear, and further clinical information is expected to help clarify appropriate treatment strategies for this patient population.

In conclusion, although DC is a rarely encountered in clinical practice and its clinical behavior has not yet been

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**Figure 2.** High-resolution computed tomography (HRCT) images of the patient. At a routine medical checkup, reticular abnormalities and ground-glass attenuations were predominantly seen in the subpleural area (A). HRCT images at the onset of acute exacerbation (three years after the routine medical checkup) showed diffuse areas of ground-glass attenuations superimposed on the underlying fibrotic reticular opacities (B).
fully clarified, physicians should keep in mind that FIP combined with DC has the potential to cause fatal acute exacerbation.

The authors state that they have no Conflict of Interest (COI).

References

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