Introduction

Interstitial lung disease (ILD) is a term that refers to a heterogeneous collection of disorders characterized by abnormal gas exchange due to altered structure of the interstitial region of the lung. ILD occurs in a variety of clinical spectrum, such as isolated pulmonary disorders, due to environmental exposures, a consequence of chemotherapy or radiation therapy, and as part of systemic diseases (autoimmune diseases or genetic disorders). In this report, we present a case series of three patients with interstitial lung disease who have specific signs and symptoms but genetically undetermined.

Case Presentations

Case 1
An 11-year-old male patient presents with fever, sputum, dyspnea, reduced oxygen saturation. Symptoms persisted despite antibiotic treatment. He was hospitalised for pneumonia twice at the ages of two and six months. His family history was unremarkable except spontaneous pneumothorax in his father. On physical examination his general condition was moderately deteriorated. He also had growth retardation, atypical face appearance, hearing loss, pectus excavatum , joint laxicity and arachnodactyly. The laboratory tests were normal. His chest X-Ray showed diffuse alveolar infiltration. On thoracic tomography he had mediastinal and hilar lymphadenopathy, subpleural apical bullae, subpleural cystic changes and signs of interstitial emphysema in pulmonary parenchyma. There were also nodules in the right lower lobe and left lower lobes. Sweat test was performed and revealed a chloride level of 47 mEq/L; echocardiogram was completely normal.

Pathology examination of the lung biopsy showed signs compatible with extrinsic allergic alveolitis.

Laboratory testing was positive for pigeon precipitating antibody. A re-questioning of his history revealed a physical contact with chickens. He was started on a steroid at a dose of 1 mg/kg/day. However, as he had subpleural cysts and
progressing bullae in lung parenchyma, his signs and symptoms were considered to be related possibly to flamin A mutation, thus a genetic analysis was ordered.

Case 2
A 9-year-old female had recurrent pulmonary infections and productive cough since the age of 2 months. There was usual interstitial pneumonia history in both grandfathers. On physical examination she had diffuse rales over the lung fields, other systems were normal. Laboratory studies were normal except high C-reactive protein level. A chest X-Ray showed diffuse alveolar infiltration in both lungs. Thoracic tomography showed millimetric nodule, alternating patchy areas of increased and decreased density. Sweat test revealed chlorid level of 27 mEq/L; an echocardiogram, and ciliary pathological examination were all normal. Respiratory function test revealed signs of restriction. The pathology examination revealed lymphoid aggregates in bronchi and around bronchioles, desquamative alveolar macrophage filling up alveolar spaces (focal desquamative interstitial pattern), edema in alveolar spaces, and atelectasis. Since her family history was positive and her signs and symptoms were compatible with the condition, flamin A, surfactant prt c, and ABCA 3 mutations were sent for analysis; although no mutation was detected.

Case 3
A 14-year-old patient presented with recurrent pulmonary infections accompanied by growth and mental retardation. She also had nephrolithiasis, and hypopigmented skin lesions. The past history was notable for pulmonary infections starting at the age of three days and recurring frequently thereafter, requiring multiple hospital admissions. Lung sounds were diminished on the basis of left lungs. A thoracic computerized tomography at the age of seven years showed volume loss and substantial cystic bronchiectatic changes in the lower lobes of both lungs, nodules in the upper lobes of both lungs and in the lower lobe of the left lung, and bullae with a maximum diameter of 2 cm in the apices of both lungs. Left lower lobectomy was performed for bronchiectasis, and the biopsy result was reported as bronchiectasis showing focal atypical features and chronic parenchymal injury. Sweat test and a swallow test were normal; immunological tests revealed high IgG and IgA but normal IgM; a normal blastic transformation, low cd16 and IgA, and normal lymphocyte subset. The patient had been started with intravenous immunoglobulin treatment. Considering cystic bullous changes in the subpleural space and joint laxity, raised a suspicion about collagen tissue disorders and prompted ordering integrin and filamin A mutation tests.

Discussion
Children’s interstitial lung diseases (chILD) might have been difficult to diagnose due to many types of the disease and wide range of underlying causes and signs and symptoms that are the same as for many other diseases. There is no pathognomonic laboratory criteria for the diagnosis of ILD in children (1).

Although genetic mechanisms underlie many chILD, pathogenesis remains uncertain for many of these disorders (2). In our cases, mutation analyses were performed for preliminary diagnoses because of consanguinity and other system involvement. Since the results were negative, whole exome sequencing (WES) was performed to the patients but no significant result could be achieved.

All genome sequences of affected children and their family members in various chILD diseases have led to the discovery of new candidate genes associated with chILD (3,4,5). Especially in familiar cases or in children of consanguineous parents, genetic diagnosis provides an useful tool to identify the underlying etiology of interstitial lung disease (6).

The knowledge of gene variants and associated phenotypes is crucial to identify relevant patients in clinical practice (6). It seems likely that there will be a number of genes that enhance susceptibility to chILD, but arguably, and more likely, polymorphisms at one or more genetic loci will affect severity and progression of disease once this is established (7).

Conclusion
To define the genetic basis and causes of interstitial lung diseases, phenotypic definitions should be made and patients with similar characteristics should be collected.

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