PRIKAZ SLUČAJA – CASE REPORT

Three cases with Intertitial Lung Disease: What are the causes?

Tri slučaja sa intersticijalnom bolesti plućai Koji su uzroci

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Summary Diagnosis of interstitial lung diseases is quite difficult in childhood. There are no firmly pathognomonic feature of the disease. Frequently, it can mimic many other lung diseases. At the same time, there are many genetically unexplained varieties, new mutations arise every day and confuse the underlying genetic basis. Therefore, in order to be able to elucidate the genetic etiology of patients with similar phenotype, clinical data should be collected and analysed. International network of the confirmed and suspected cases should be established
In this case series, we report three children with interstitial lung disease who had similar clinical findings and family histories but genetically remained unexplained.

Key words:Interstitial lung diseases, genetics, etiology, childhood

Sažetak Dijagnoza intesticijalne bolesti pluća je teška kod dece, s obzirom da sigurnih pokazatelja bolesti nema i često klinička slika podseća na mnoge druge bolesti pluća.Takodje, u praksi se susrećemo sa genetski neobjašnjivim varijetetima, nove mutacije, koje se pojavljuju, dodatno stvaraju konfuziju. Ovo su razlozi za prikupljanje kliničkij ekspresija bolesti i povezivanje genetskih faktora kod pacijenata sa sličnim fenotipovima. Internacionalno prijavljivanje potvrđenih i sumnjiovih slučajeva moglo bi pomoći u boljem sagledavanju problema.
Prikazujemo tri pacijenta sa intersticijalnom bolesti pluća, koji imaju sličnu kliničku sliku i porodičnu istoriju, a genetski su ostali neobješnjeni.

Ključne reči:Intersticijalna bolest pluća, genetika, etiologija, deca

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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 presnets 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.
His hearing tests showed bilateral mild-to-moderate hearing loss. Respiratory function tests showed restriction. 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 aggregates 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, filamin 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 cd 16-56, low cd19, and a normal lymphocyte subset. The patient had been started with intravenous immunoglobulin treatment.

During the investigation of developmental delay, cranial MRI was performed and revealed that the right parietal areas of infarction disappeared without leaving any sequela but there was a sequela hemorrhagic lesion in the right thalamus and areas of paramagnetic substance accumulation in both globus pallidi.

Considering cystic bullous changes in the subpleural space and joint laxicity, 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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References:

1. Hilman BC. Diagnosis and treatment of ILD. Pediatr Pulmonol. 1997 Jan;23(1):1-7.
2. Young LR, Trapnell BC, Mandl KD, Swarr DT, Wambach JA, Blaisdell JC. Accelerating Scientific Advancement for Pediatric Rare Lung Disease Research. Report from a National

Institutes of Health–NHLBI Workshop, September 3 and 4, 2015. Ann Am Thorac Soc. 2016 Dec; 13(12): 385–393.
3. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, Smolarek T, Dishop MK, Wert SE, Whitsett JA, *et al*. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. *J Exp Med* 2008;205:2703–2710.
4. Nogee LM, de Mello DE, Dehner LP, Colten HR. Brief report: deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 1993;328:406–410.
5. Hamvas A, Deterding RR, Wert SE, White FV, Dishop MK, Alfano DN, Halbower AC, Planer B, Stephan MJ, Uchida DA, *et al*. Heterogeneous pulmonary phenotypes associated with mutations in the thyroid transcription factor gene NKX2-1. *Chest*2013;144:794–804.
6. Hartl D, Griese M. Interstitial lung disease in children – genetic background and associated phenotypes. Respir Res. 2005; 6(1): 32
7. du Bois RM. The genetic predisposition to interstitial lung disease: functional relevance. Chest. 2002 Mar;121(3 Suppl):14S-

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