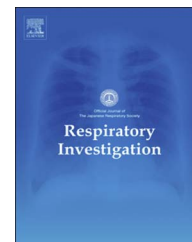




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Original article

Is hypothyroidism in idiopathic pleuroparenchymal fibroelastosis a novel lung-thyroid syndrome?

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ABSTRACT

Background: Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare type of interstitial pneumonia characterized by fibroelastosis. Patients with IPPFE as well as idiopathic interstitial pneumonia often have autoimmune diseases, which sometimes coincide with hypothyroidism (HypoT). However, there have been no reports on the association between IPPFE and HypoT. The purpose of this study was to evaluate the correlation between IPPFE and HypoT. We also examined the pathological features of the thyroid glands from autopsied cases.

Methods: Thirteen patients diagnosed with IPPFE from among 255 consecutive cases of idiopathic interstitial pneumonia were included in this study; pertinent data were obtained from our hospital's clinical library. We examined the prevalence of HypoT and compared the clinical, radiological, and pathological features between the patients with and those without HypoT. Histological analyses of the lungs and thyroid glands were performed in 4 and 3 cases, respectively.

Results: HypoT was identified in 7 of 13 patients (53.8%). Sex, body mass index, survival time, and laboratory test results were not significantly different between patients with and those without HypoT. Radiological and pathological lung findings were similar between both groups of patients. Thyroid gland histology demonstrated perifollicular or interlobular fibrosis without inflammation in all three cases, including a euthyroid case.

Conclusions: Although we only analyzed a small number of IPPFE cases, HypoT was

Abbreviations: BMI, body mass index; FVC, forced vital capacity; HRCT, high-resolution computed tomography; HypoT, hypothyroidism; IPF, idiopathic pulmonary fibrosis; IPPFE, idiopathic pleuroparenchymal fibroelastosis; KL-6, Krebs von den Lungen-6; NTI, nonthyroidal illness; PPFE, pleuroparenchymal fibroelastosis; RV/TLC, residual volume to total lung capacity; SP-D, surfactant protein-D; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTF, Thyroid transcription factor; UIP, usual interstitial pneumonia; VATS, video-assisted thoracic surgery

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prevalent among all of them. Characteristic fibrosis in the thyroid gland was observed even in a euthyroid case. Therefore, patients with IPPFE may potentially have thyroid gland dysfunction through a common pathogenesis in both organs.

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1. Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare interstitial pneumonia that was first reported by Frankel et al. in 2004 [1]. Recently, IPPFE was classified as rare idiopathic interstitial pneumonia [2]. The clinical, radiological, and pathological features of IPPFE have been studied recently. Although the etiology of IPPFE is unknown, many patients with pleuroparenchymal fibroelastosis (PPFE) have underlying conditions, such as connective tissue disease [3]; ankylosing spondylitis [4]; bone marrow or lung transplantation [5,6]; or drug-induced lung diseases, including cyclophosphamide [7], hypersensitivity pneumonia [8], pulmonary mycobacterial disease [9], *Aspergillus* infection [10], and asbestos-induced lung diseases [11]. These diseases sometimes represent characteristic features of PPFE.

Connective tissue diseases can also be associated with other interstitial diseases. For example, patients with rheumatoid arthritis often develop usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia [12]. Chronic autoimmune thyroiditis, or Hashimoto's thyroiditis, is an autoimmune disease in which the thyroid gland is gradually destroyed, leading to hypothyroidism (HypoT). Recently, the correlation between HypoT and idiopathic pulmonary fibrosis (IPF) was reported [13]. The study revealed that patients with IPF had a higher prevalence of HypoT than those with chronic obstructive pulmonary disease and healthy controls. However, the association between IPPFE and HypoT has not yet been reported. The exact cause of IPPFE remains unclear, although one hypothesis is that it is an autoimmune disorder. In many previous studies, increased levels of autoantibodies in IPPFE patients have been reported [14]. However, there is no data on the association between thyroid disease and IPPFE.

The aim of this study was to assess whether HypoT is associated with IPPFE and to compare the clinical and radiological characteristics between IPPFE patients with and those without HypoT. We also examined the pathological features of thyroid glands from autopsied cases.

2. Patients and methods

2.1. Study population

We retrospectively reviewed medical records of patients who attended the Japanese Red Cross Medical Center, Tokyo, Japan, from January 1, 2006 to October 31, 2016. We searched for the radiological and pathological records of patients with idiopathic interstitial pneumonia using the terms “idiopathic interstitial pneumonia,” “atelectatic fibrosis,” “intra-alveolar

fibrosis,” “pleuroparenchymal fibroelastosis,” and “idiopathic pulmonary upper lobe fibrosis.” A total of 255 consecutive patients with idiopathic interstitial pneumonia were selected and then assessed for IPPFE using the criteria below.

2.2. Assessment personnel

Three pulmonologists reviewed the clinical characteristics, two pulmonologists and one radiologist evaluated the computed tomography scans, and two pathologists assessed the pathological findings.

2.3. Inclusion and exclusion criteria

The diagnosis of IPPFE was based on clinical and radiological data with or without pathological data. Cases were included when a definite or consistent diagnosis of IPPFE was made according to radiological and/or pathological criteria [1,8,15]. Patients whose clinical data were unavailable were excluded. If the pulmonologists, radiologists, or pathologists classified findings as inconsistent with a diagnosis of PPFE, the case was excluded. Patients with connective tissue disease, except autoimmune thyroiditis, sarcoidosis, ankylosing spondylitis, post-radiation pulmonary fibrosis, bone marrow or lung transplantation, drug-induced lung disease, hypersensitivity pneumonia, pulmonary mycobacterial disease, *Aspergillus* infection, asbestos-induced lung diseases, or other forms of secondary PPFE, were excluded.

2.4. Clinical analyses

Body mass index (BMI), smoking history, past medical history, cause of death, laboratory data, and pulmonary function tests were reviewed from medical records. In most patients, pulmonary function tests were performed according to guidelines [16] at diagnosis and repeated at least once. At the first visit, the levels of thyroid hormones and autoimmune antibodies, such as antinuclear, anti-thyroid peroxidase (anti-TPO), and antithyroglobulin antibodies, were measured for assessment of interstitial pneumonia. All laboratory data were obtained at diagnosis, before IPPFE treatment. None of the patients had congenital thyroid disease or took medications known to deteriorate thyroid function (i.e., amiodarone or interferon- γ). HypoT was confirmed in patients with elevated thyroid-stimulating hormone (TSH) and normal or decreased free thyroid hormone levels. Hashimoto's thyroiditis was diagnosed when elevated levels of anti-TPO and/or antithyroglobulin antibodies were found and when hypoechogenicity of the thyroid gland was detected via ultrasound. Subclinical HypoT was defined as a serum TSH level above

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