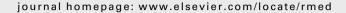


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# Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias

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#### **KEYWORDS**

Antisynthetase syndrome; Aminoacyl-tRNA synthetase; Idiopathic interstitial pneumonia; Nonspecific interstitial pneumonia

#### Summary

Objectives: Antisynthetase syndrome (ASS) is characterized by autoantibodies to aminoacyltRNA synthetases (anti-synthetase) and it is frequently associated with interstitial lung disease. The purpose of this study was to elucidate the prevalence and characteristics of the anti-synthetase positive subpopulation among idiopathic interstitial pneumonias (IIPs) and to clarify the importance of screening for these antibodies.

*Methods*: A retrospective study was performed in 198 consecutive cases with IIPs. Screening for six anti-synthetase antibodies was performed in all cases. Clinical profiles of all cases were compared with reference to the presence of anti-synthetase. High-resolution computed tomography (HRCT) findings of anti-synthetase positive cases were also analyzed.

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Results: 13 cases (6.6%) were positive for anti-synthetase. Anti-EJ was most prevalent, followed by anti-PL-12. Onset ages of anti-synthetase positive cases were younger than those of anti-synthetase negative cases. Extrapulmonary features of ASS were absent in 6 anti-synthetase positive cases (46.2%). Histologically, among 5 UIP with lymphoid follicles and 11 NSIP cases, the prevalence of anti-synthetase positive cases was 8/16 (50%). On HRCT, ground glass opacity and traction bronchiectasis were the major findings in anti-synthetase positive cases, while honeycombing was absent.

Conclusions: Anti-synthetase positive cases were not rare among IIPs. Anti-synthetase should be screened for in IIPs, especially in pathological NSIP or UIP with lymphoid follicles. These patients should be screened for anti-synthetase even if no suggestive extrapulmonary manifestation exists.

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#### Introduction

Interstitial lung disease (ILD) is caused by both known and unknown etiologies, and idiopathic interstitial pneumonias (IIPs) are the most prevalent type of ILD. Connective tissue disease (CTD) affects a wide variety of organs with the incidence of pulmonary involvement ranging from 19 to 67%. A thorough etiological work-up of CTD and its related conditions is essential in clinical practice for ILD. Difficult-to-diagnose cases exist when they have an incomplete form of CTD that cannot be categorized as CTD using a range of specific criteria. These cases are categorized as idiopathic, or sometimes unclassifiable.

The aminoacyl-tRNA synthetases are a family of enzymes, each of which catalyses the formation of aminoacyl-tRNA from a specific amino acid and its cognate tRNA. Autoantibodies to eight of these synthetases (anti-synthetase) have been reported and they are defined as myositis-specific autoantibodies.3 Clinical features that occur in antisynthetase positive cases include myositis, ILD, arthritis, mechanic's hand and often Raynaud's phenomenon. Combination of positive anti-synthetase antibody with any of these findings constitutes a distinct syndrome named antisynthetase syndrome (ASS).4 The prevalence of antisynthetase among PM/DM is 30-40% and characteristics of anti-synthetase positive populations have been established in the past, in several myositis-based large cohort studies. In particular, subpopulations of patients with myositis have higher rates of ILD when they have anti-synthetase than those who have not. 5 ILD in ASS may also be indistinguishable from IIPs when patients have minimal or no myositis. ASS comprises a distinct disease entity and demonstrates a generally good response to corticosteroids, though a number of cases show recurrence after withdrawing or reducing doses of corticosteroids.<sup>6,7</sup> Fisher et al. retrospectively assessed 37 patients with IIPs who had some signs or symptoms indicative of ASS, but were not positive for ANA or anti-Jo-1 antibody, and found that 9 (24%) patients were positive for anti-synthetase.8 In this previous study, antisynthetase were measured in patients with clinical signs indicative of ASS, and the decision to perform the test depended upon each physician; thus the overall prevalence of anti-synthetase among IIPs was not clarified. The characteristics of patients with anti-synthetase positive IPs are still unknown together with identification of the population which should be examined for these antibodies. This study aimed to investigate the prevalence of an anti-synthetase positive subpopulation among IIPs. Six anti-synthetase antibodies were measured and aspects of the clinical, pathological and radiological features of anti-synthetase positive cases were investigated to determine which patients should be screened for these antibodies.

#### **Methods**

#### Patient recruitment

In this study, idiopathic interstitial pneumonia (IIP) was defined as interstitial pneumonias of unknown cause where a patient did not fulfill classification criteria for any specific CTD or vasculitides, and in whom lung diseases were not potentially caused by drug or occupational-environmental exposures. Screening for CTD was initially performed by experienced pulmonologists, and also by rheumatologists in patients with serological or clinical features suggestive of CTD.9-16Provisionally, undifferentiated connective tissue disease (UCTD)<sup>17</sup> were not excluded from the study population. In all patients diagnosed with idiopathic interstitial pneumonias (IIPs) who visited Kyoto University Hospital from July 2007 through April 2009 and Tenri Hospital, the tertiary care center from April 2006 through April 2009, serum samples were consecutively collected and patients were recruited into this study. The study population comprised 198 cases with IIPs, 53 with idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) (30 by histological diagnosis; 23 by clinical diagnosis), 11 with nonspecific interstitial pneumonia (NSIP), 3 with histologically unclassifiable interstitial pneumonia, and 131 with non-UIP without histology. Written informed consent was obtained from the participants, and the study was approved by the Review Board of the Ethical Committee of each Institute.

#### Data collection

Clinical information was retrospectively obtained from medical records. The data included patient's age at onset, gender, pulmonary or extrapulmonary manifestations including signs or symptoms of CTD, laboratory data results including CTD-specific autoantibodies, blood gas analysis, pulmonary function test results, bronchoalveolar lavage

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