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A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease

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ABSTRACT

Background: The relationship between the histological pattern and survival in systemic sclerosis-associated interstitial lung disease (SSc-ILD) is unclear. In patients with SSc-ILD, we investigated whether the clinical data obtained by non-invasive examinations could be used for prognostic evaluation, and attempted to clarify whether complicating acute exacerbation (AE) and the selection of pharmacological therapy were associated with survival.

Methods: Thirty-five patients with SSc-ILD, who had not been diagnosed by surgical lung biopsy were analyzed, retrospectively. The HRCT findings were evaluated by 2 radiologists and classified into "CT-UIP" or "CT-inconsistent with UIP" patterns based on whole lung interpretations. HRCT scores were calculated based on the extent of abnormality evidenced by HRCT. The log-rank test was used to determine variables, including clinical parameters and histories.

Results: Twelve (34%) of the 35 patients died during a median follow-up period of approximately 7.9 years. The log-rank test showed that a higher mortality was associated with higher age, a CT-UIP pattern, a higher score for ground-glass attenuation with traction bronchiectasis on HRCT, and complicating AE, whereas a lower mortality was significantly associated with the use of immunosuppressants. A CT-UIP pattern was significantly associated with a higher incidence of later AE.

Conclusion: Treatment with immunosuppressants was associated with a longer survival, and complicating AE is a predictor of shortened survival in SSc-ILD patients. Among the clinical parameters determined by non-invasive examinations, a CT-UIP pattern and the extent of fibrotic lesions on HRCT, but not a histological pattern of UIP, may be predictors of shortened survival.

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1. Introduction

Interstitial lung disease (ILD) is the most common complication of systemic sclerosis (SSc), occurring in approximately 80% of cases, and is a significant cause of morbidity and mortality [1]. Idiopathic interstitial pneumonias (IIPs) are classified on the basis of surgical lung biopsy (SLB) into 7 histopathological patterns, including idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), nonspecific interstitial pneumonia (NSIP), and others [2,3]. The prognoses of these histological subgroups differ. IPF/UIP has a grave prognosis with a 5-year mortality rate of approximately 60–80% [4], whereas idiopathic NSIP has a better prognosis, with a corresponding mortality rate of 14–36% [4,5]. SLB, rather than transbronchial lung biopsy (TBLB), is thought to be necessary to classify these histologic patterns of IIPs. Connective tissue disease-associated ILD (CTD-ILD) is classified into histological subgroups based on the classification of IIPs. In contrast to IIPs, the correlation between the histological pattern and survival of CTD-ILD patients may be weaker than is the case for IIPs. Park et al. reported that there was no significant difference in survival between NSIP and UIP-like ILD patients with CTD including SSc and others [6]. Bouros also showed that survival was not associated with the histological pattern of ILD (UIP or NSIP patterns) in SSc-associated ILD (SSc-ILD) [1]. Therefore, the histopathological findings of CTD-ILD are thought to be of less prognostic significance. In addition, not all patients can undergo SLB because it is an invasive procedure performed under general anesthesia. In contrast, previous sporadic studies have reported significant factors associated with the prognosis in SSc-ILD, such as the findings of a pulmonary function test (PFT), bronchoalveolar lavage fluid (BALF) analysis, and high-resolution chest CT (HRCT) [1,7–10]. The evaluation of prognostic predictors obtained by such non-invasive examinations is thus important in SSc-ILD.

SSc-ILD is a disease refractory to pharmacological therapies. Although patients with SSc-ILD are frequently treated with corticosteroid and/or immunosuppressants including CPA, CsA, and AZP [11–15], no standard pharmacological therapy for SSc-ILD has yet been established.

Acute exacerbation (AE) is a fatal event in IIPs and CTD-ILD. AE is characterized by acute deterioration of respiratory status, with new development of bilateral ground-glass attenuations (GGA) and/or consolidations on a background fibrotic area on a chest HRCT. The reported incidence of AE is 9.6–12.5% per 2 years in IPF and 1.25–4.2% per year in CTD-ILD [16–18]. A recent study found that patients with SSc-ILD can also experience AE [19]. AE in patients with IPF and CTD-ILD has been shown to be associated with shorter survival. However, no detailed report has clarified the incidence of AE and its associated risk factors in SSc-ILD patients.

In the present study, we retrospectively investigated whether the clinical data obtained by non-invasive examinations and clinical histories, such as the type of treatment and complicating AE, would be associated with the clinical outcome of patients with SSc-ILD.

2. Patients and methods

2.1. *Patients*

We retrospectively reviewed the medical records and HRCT images covering the period between January 1990 and December 2010 for all patients with SSc-ILD. We diagnosed 59 cases of SSc-ILD during this period. In order to analyze the long-term outcomes, we studied 35 patients with SSc-ILD for whom a follow-up between 5 and 15 years was possible. We set the minimum observation period at 5 years, as this represented the 25th percentile of the overall observation period. We excluded 20 patients who dropped out within the minimum observation period after the first observation day. To investigate the mortality of interstitial lung disease, we excluded 4 patients who died of cancer.

To qualify for inclusion, patients had to (*a*) fulfill the American Rheumatism Association preliminary criteria for SSc [20,21], (*b*) show features suggestive of ILD on HRCT images, and (*c*) have no other conditions such as infection, congestive heart failure, or hypersensitivity pneumonia. We defined the first observation date as the day of diagnosis of ILD. Overall survival (OS) was defined as the period of survival

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