Coexistence of Autoantibodies against the Golgi Complex and Ro52 Antigen in a Patient with Nonspecific Interstitial Pneumonia

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Abstract

Nonspecific interstitial pneumonia (NSIP) is often associated with connective tissue diseases (CTD). The diagnosis of NSIP was confirmed in a 63-year-old man by high-resolution computed tomography and an open lung biopsy. Anti-Golgi complex autoantibodies (AGA) and anti-Ro52 antibodies were simultaneously detected at high concentrations. Autoantibodies to aminoacyl-tRNA synthetases (ARS) were negative. The patient was treated with corticosteroids for six months. During the seven-year follow-up, NSIP had a slow progression and patient had not developed the clinical features of CTD. The present study potentially demonstrates that the autoimmune process elicited by AGA and/or Ro/SSA may play a role in promoting idiopathic NSIP independently of the typical ARS routes, which has not been reported thus far.

Key words: anti-Golgi complex antibodies, nonspecific interstitial pneumonia

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Introduction

Anti-Golgi complex autoantibodies (AGA) are considered to be rare. Rossie et al. (1) found a prevalence of only 0.1% in more than 1,000 patients with connective tissue diseases (CTD). In another study conducted by Hong et al. (2) only 12 AGA positive sera out of 5,983 consecutive patients was observed. In the largest series reported to date, AGA were found in 13 out of 9,841 patients with rheumatic diseases (3).

Autoantibodies directed against the Golgi complex were first identified in the serum of a Sjögren’s syndrome (SS) patient with lymphoma (4). Subsequent reports have described AGA typically in a high titer, in the patients with systemic rheumatic diseases, including SS (5), systemic lupus erythematosus (SLE) (6), rheumatoid arthritis (RA) (7) and inflammatory myopathies (8). In addition, AGA were found to be associated with viral infections (9, 10), in particular during pegylated interferon therapy (11). Their presence during viral infection is transitory, and the titer is generally low (12).

There are very limited reports of interstitial pneumonia associated with AGA. All of the previously reported cases had established CTDs: SLE, SS and polymyositis (PM) (1, 3), SLE and RA (5), and RA and PM (13).

The American Thoracic Society/European Respiratory Society International Consensus Classification panel identified the clinical entity of idiopathic nonspecific interstitial pneumonia (NSIP) as a provisional diagnosis and recommended further studies. Moreover, NSIP may precede the appearance of CTD by several months or years (14, 15).

We herein report a case with AGA who presented with NSIP diagnosed during an open lung biopsy, which did not exhibit the clinical symptoms of myositis or any other CTD during a seven-year follow-up period.
A physical examination revealed fine crackles audible at both lung bases. There was no photosensitivity, rash, hyperkeratosis of the fingers or other skin lesions, arthritis or Raynaud’s phenomenon. High-resolution computed tomography (HRCT) of the chest showed bilateral, predominantly right-sided, lower lung ground-glass and reticular opacities and bronchial dilatation (Fig. 1A). Pulmonary function tests (PFT) revealed a mild restrictive impairment and reduced diffusing capacity for carbon monoxide (DLco) (Table 1). An arterial blood gas measurement revealed mild hypoxemia (pO₂=9.5 kPa) with normocapnia at rest. An electrocardiogram, echocardiogram and abdominal ultrasound showed no abnormal findings.

The laboratory tests showed leukocytosis and elevation of the serum C-reactive protein level and the erythrocyte sedimentation rate (ESR) (Table 1). No pathologic findings were found regarding other biochemical parameters including creatine kinase, lactate dehydrogenase, electrolytes,
angiotensin-converting enzyme, IgM rheumatoid factor, IgG, IgA, IgM, C3 and C4 and various other parameters [including anti-HIV, anti-hepatitis C virus (HCV), hepatitis B virus surface (HBs) antigen and syphilis serology].

Indirect immunofluorescence (IIF) on human epithelial type-2 (HEp-2) cells as the substrate showed staining of a polar organelle adjacent to the nucleus and composed of irregular large granules, characteristic of the Golgi complex pattern (Fig. 2) at a titer of 1/640. Anti-Ro/SSA antibodies were found to be positive, as assessed with an enzyme-linked immunosorbent assay (ELISA) at 84.3 U/mL (normal value <25 U/mL). However, antibodies directed against other extractable nuclear antigens (ENA), dsDNA, cardiolipin, anti-citrullinated protein antibodies (ACPA), and anti-neutrophil cytoplasmic antibodies (ANCA) were not detected.

The pathologic findings obtained in a transbronchial lung biopsy were not conclusive. Therefore, at the end of 2007 an open lung biopsy was performed. Two lung biopsy specimens, measured up to 25 mm, were obtained. Microscopically, the architecture of the lung was mainly preserved, but the alveolar spaces were mildly distorted and covered by hyperplastic pneumocytes containing foamy macrophages mixed with mucus. Diffuse interstitial chronic inflammatory cell infiltration was associated with mild to moderate fibrous thickening. Foci of the follicular lymphoid aggregates could additionally be seen, as well as perivascular and peribronchial lymphocytic infiltration. Specific granulomatous disease and malignancy were not diagnosed (Fig. 3). These findings were summarized as a predominant cellular pattern consistent with the proposed histological features of the NSIP (14).

Further clinical investigations were conducted in order to exclude underlying CTD and other possible causes or associations of NSIP and to disclose the presence of diseases previously reported to be associated with AGA and anti-Ro/SSA antibodies. Possible causes of NSIP, such as drug reactions, extrinsic allergic alveolitis or infection, were excluded. Systemic screening of malignancies was negative. Sjögren’s syndrome was excluded by the absence of ocular and oral symptoms, normal results of Shirmer’s test and salivary scintigraphy. A neurological examination revealed normal muscle tone and strength, the absence of muscle pain, tenderness and muscle fatigue. Furthermore, a myopathic lesion was excluded by electromyography (EMG) and normal enzyme levels in the serum. Naïfold capillaroscopy revealed a normal pattern. There were no symptoms or clinical signs of hepatic disease and/or any other CTD.

The patient was diagnosed with NSIP according to the laboratory signs of inflammation, and we initiated treatment with oral prednisone, 0.5 mg/kg body weight per day with a gradual tapering. Six months after the initiation of treatment there was an improvement in the symptoms and pulmonary function. The laboratory tests revealed decreased values of the ESR and C-reactive protein (CRP) levels and PFT indicated an approximate 20% improvement in the forced vital capacity (FVC) and DLCO (Table 1). Thereafter, the patient decided to discontinue prednisone therapy.

The patient was followed up without treatment until March 2012, by which time the total lung capacity (TLC), FVC, and DLco were moderately improved (Table 1). During the clinical course, the patient has not noticed a worsening of dyspnea. The CT scan obtained approaching the five-year follow-up showed a modest increase in the areas of ground-glass attenuation and the progression of bronchiectasis (Fig. 1B).

Although there were no clinical symptoms suggestive of CTD and no specific autoantibodies for the corresponding CTD were found, there was still a possibility of interstitial pneumonia in the context of myositis. Nevertheless, by line blot tests we could not identify the presence of myositis-specific antibodies: anti-Jo-1 (histidyl-), anti-PL-7 (threonyl-), anti-PL-12 (alanyl-), anti-EJ (glycol-), anti-OJ (isoleucyl-tRNA synthetase), anti-SRP (signal recognition particle) and anti-Mi-2; however, myositis-associated antibody and anti-Ro52 was found at high concentrations.

At the last visit in June 2014, the patient was observed to be in a clinically stable condition with no exertional dyspnea and without decline in the pulmonary function (Table 1). There were no signs of right ventricular overload by echocardiography. Anti-KS (asparaginyl-tRNA synthetase) antibodies were measured by the radioimmuno assay (RIA) method and the patient was found to be negative with a value of 6.86 (reference value <10, gray zone <15). Moreover, AGA were detected by IIF at a titer of >1:10,000.

Discussion

We herein report the case of isolated interstitial pneumonia of NSIP pattern associated with AGA and anti-Ro52 antibodies. The clinical presentation, radiological findings, histological characteristics and disease progression are in accordance with the diagnosis of NSIP (14). From the current viewpoint, NSIP is recognized as a distinct clinical entity with a more favorable prognosis than idiopathic pulmonary fibrosis (15).
It is recognized that the rate of progression of pulmonary fibrosis is highly variable, and controversy exists regarding the timing of treatment. In the present case we initiated corticosteroid therapy in the early, so-called inflammatory stage with the hope of slowing the disease progression. The initial response occurred within the first months of initiating therapy. Due to patient’s decision to discontinue immunosuppressive treatment we had the unique opportunity to observe the natural course of the disease. Despite the radiographic progression, the patient’s condition continues to remain unchanged, and the results on PFT actually slightly improved during the long follow-up period. The differences in behavior may reflect the clinical variability in the clinicoradiopathologic entity of NSIP. By definition, NSIP has a pattern that may be diffuse or patchy in its distribution. Previous studies clearly demonstrated the superior sensitivity of HRCT compared with PFT for the early detection of interstitial lung disease (ILD). Thereafter, only a higher HRCT fibrotic score was found to be independently associated with mortality. Then, it was suggested that only changes in the

Table 2. Clinical and Laboratory Findings of Reported Cases with Simultaneous Presence of Antibodies against Golgi Apparatus and Ro(SSA) Antigen and Present Case.

| Clinical presentation | Patient 1 [1] | Patient 2 [20] | Patient 3 [13] | Patient 4 [21] | Patient 5 [8] | Present case |
|-----------------------|---------------|----------------|----------------|----------------|----------------|--------------|
| Age and sex           | 73 F          | 44 F           | 61 F           | 59 F           | 71 F           | 62 M         |
| Anti-Golgi antibody   | +             | +              | +              | +              | +              | +            |
| Anti-Ro(SSA) antibody | +             | +              | +              | +              | +              | +            |
| Anti-dsDNA antibody   | -             | -              | -              | ND             | -              | -            |
| Myositis–specific antibodies | ND            | ND             | ND             | ND             | -              | -            |
| Response to steroids  | +             | +              | ?              | -              | +              | +            |

ND: not determined, SLE: systemic lupus erythematosus, SS: Sjögren’s syndrome, NSIP: non-specific interstitial pneumonia
FVC were strongly predictive of the long-term survival in the patients with well-defined NSIP. In contrast, serial changes in the DLco, and HRCT are of more limited value (16).

The diagnosis of idiopathic ILD is typically made after excluding CTD among other conditions. It has been shown that NSIP is one of the most common patterns of ILD in the patients with a variety of CTD, including scleroderma, RA, PM and SS. Although in most patients with a CTD and respiratory symptoms the systemic nature of the disease is obvious, pulmonary manifestations may often dominate the clinical picture or precede the systemic findings. In this setting, clues to an underlying CTD may be entirely absent or include subtle findings from various systems, including skin, vascular and musculoskeletal systems or internal organs (17). A recent review of 67 patients with definitive NSIP demonstrated the presence of antinuclear antibodies in 43% of the patients with subsequently manifested CTD in two patients (1 scleroderma and 1 polymyositis) (15). Although idiopathic NSIP appears to have the same prognosis as NSIP associated with CTD (18), the potential for systemic disease to involve multiple organ systems augments to the morbidity and mortality.

Bizzaro et al. (12) previously reported that the presence of high titer AGA may constitute an early sign of systemic autoimmune disease, even in the absence of clinical manifestations. Conversely, the findings of a retrospective study (19) demonstrated that AGA are not clinically associated with the diagnosis of systemic autoimmune disease.

To the best of our knowledge, the simultaneous presence of AGA and anti-Ro/SSA was reported in only previous five cases (1, 8, 13, 20, 21) (Table 2). All of the reported cases manifested myopathy and, with one exception, responded well to steroid therapy.

It has been proposed that many intercellular autoantigens, such as Ro, are translocated to apoptotic blebs and may trigger autoantibody production. Conversely, Golgi autoantigens are cleaved during apoptosis and necrosis and are not localized to the apoptotic blebs. The released modified Golgi autoantigens may stimulate the autoantibody responses if they are presented to the immune system in proinflammatory context (22). Once produced, antibodies against the Golgi and Ro antigens may in fact act in synergy to induce cellular damage and release more autoantigens. The autoimmune process elicited by AGA and anti-Ro may play a substantial role in promoting idiopathic NSIP with no conspicuous systemic involvements (especially myositis) in some cases.

Several researchers have emphasized the importance of autoantibodies to aminocyl-tRNA synthetases (ARS), including anti-OJ and anti-KS antibodies for promoting idiopathic interstitial pneumonia, including NSIP without myositis (23-26). It appears likely that tRNA synthetases play a direct role in the induction and maintenance of autoimmunity. In fact, lung involvement appears to be even more strongly associated with these autoantibodies than muscles. ILD often precedes myositis symptoms, which raises the possibility of an immune reaction initiating in the lungs, possibly after the exposure to environmental factors such as viral infections or smoking. A proteolytically sensitive conformation of the histidyl-tRNA synthetase has been demonstrated in the lung, which suggests that autoimmunity to histidyl-tRNA synthetase is initiated and propagated in the lung (27).

The negative results for anti-KS and anti-OJ antibodies in the present case suggest that the AGA- and/or Ro-associated autoimmune process importantly functions as one of the autoimmune pathways for the pathogenesis of idiopathic NSIP independently of the OJ and KS routes.

Moreover, it was shown that the coexistence of anti-SSA and anti-Jo-1 antibodies represents a good predictor for severe ILD in the patients with myositis who require a more aggressive approach in therapy (28). On the contrary, the simultaneous presence of anti-SSA and AGA was characterized by a favorable clinical course in the present case. The mechanism for the coupling of the antibody response remains elusive, however, it is likely to play a fundamental role in the disease pathogenesis and prognosis.

In the present case, neither clinical symptoms nor specific autoantibodies suggestive of the presence of a variety of CTD were found during the seven-year follow-up period. However, the possibility of future CTD could not be fully ruled out.

It appears that NSIP is in fact not a single condition, but has a variety of subtypes which are associated with very different prognoses. The present case potentially demonstrated a particular autoimmune process related to the pathogenesis of idiopathic NSIP, which has not yet been reported.

The authors state that they have no Conflict of Interest (COI).

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