Pulmonary Arterial Hypertension and Severe Pulmonary Fibrosis in Systemic Sclerosis Patients with a Nucleolar Antibody

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ABSTRACT. ***Objective.*** Pulmonary arterial hypertension (PAH) and severe pulmonary fibrosis (SPF) are the most common causes of death in scleroderma. Our study focuses on lung disease in patients with a nucleolar antibody in comparison to other scleroderma-specific autoantibodies.

Methods. Patients initially seen between 1972 and 1995 (and followed through 2004) with PAH [systolic pulmonary artery pressure (sPAP) > 50 mm Hg] or SPF [forced vital capacity (FVC%) < 55% predicted) were grouped by the presence of anticentromere antibody (ACA), an isolated antinucleolar antibody (ANoA), or an antitopoisomerase antibody-I (TOPO).

Results. Twenty percent of ACA, 23% of TOPO, and 32% of ANoA patients had severe lung disease ($p < 0.005$). In ANoA patients with PAH without severe fibrosis, the FVC was lower (71% predicted) than in ACA patients, suggesting they had some interstitial fibrosis. However, they had a higher FVC%/diffusing capacity for carbon monoxide (DLCO)% ratio than the ACA patients (2.4 vs 1.8). Pulmonary hypertension in TOPO patients was associated with a lower FVC%/DLCO% ratio and lower levels of PAP than either the PAH in ACA or ANoA patients.

Conclusion. Scleroderma-specific autoantibodies are associated with characteristic subgroups of lung disease. The ANoA patients have a unique mixture of PAH and SPF subgroups of lung disease. Scleroderma-specific autoantibodies and the FVC%/DLCO% ratio are helpful in determining whether a patient has PAH alone, PAH along with pulmonary fibrosis, or secondary PAH from chronic hypoxia with SPF. (First Release Oct 15 2007; J Rheumatol 2007;34:2230–5)

Key Indexing Terms:

SCLERODERMA SYSTEMIC SCLEROSIS PULMONARY FIBROSIS
PULMONARY HYPERTENSION NUCLEOLAR ANTIBODIES AUTOANTIBODIES

Today, pulmonary arterial hypertension (PAH) is the most common cause of death in scleroderma[1]. Classically, this complication occurs as an isolated primary vasculopathy in patients with longstanding limited cutaneous disease and minimal or no interstitial fibrosis. However, the more frequent use of high resolution computerized tomography (CT) scans and more careful evaluation of lung disease in general has shown that many of these patients also have some interstitial disease. In the past, PAH was always a progressive and uniformly fatal disorder so that making this diagnosis was not meaningful for the patient. The recent availability of effective treatments for PAH has made it necessary to measure pulmonary artery pressures in patients with systemic sclerosis (SSc).

Chang and colleagues reported that 18% of 618 scleroderma patients had evidence of both restrictive lung disease and pulmonary vasculopathy[2]. Some of these patients likely had severe fibrosis and secondary (hypoxic) pulmonary hypertension (PH), while others may have had severe "isolated" PAH with mild pulmonary fibrosis. Since the treatment of these 2 subgroups of lung problems is very different, it is important that patients with SSc are carefully evaluated to determine which type of lung disease they have.

We and others have shown that several of the SSc-specific serum autoantibodies are associated with certain types of scleroderma lung disease[3-10]. Classically, anticentromere antibody (ACA) is associated with isolated or vasculopathic PAH and antitopoisomerase I antibody (TOPO) with severe pulmonary fibrosis (SPF)[11]. The less common antibodies with a nucleolar staining pattern are associated with both SPF and PAH[12-15]. The purpose of our study was to focus on the lung disease in patients with a nucleolar staining pattern, to compare these manifestations to patients with ACA and TOPO, and to point out the differences in the type of PH seen in these patients.

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MATERIALS AND METHODS

Patients. Eligible patients with SSc were those first evaluated at the University of Pittsburgh between January 1, 1972, and December 31, 1995. These patients were followed yearly with a 93% accountability as of 2002. We specifically identified patients with severe lung disease including PAH or SPF. Patients had one of the following criteria: (1) forced vital capacity (FVC) less than 55% predicted; (2) pulmonary fibrosis as the cause of death; (3) systolic pulmonary artery pressure (sPAP) greater than 50 mm Hg on echocardiogram; (4) a mean pulmonary artery pressure (PAP) greater than 25 mm Hg on right heart catheterization; or (5) death from PAH[1]. Patients with PAH from other causes such as renal crisis, left-sided heart disease, diastolic dysfunction, or other cardiac disorders were excluded. Not all patients had high resolution CT scans, so this was not used as a criterion. Patients who died of PAH or pulmonary fibrosis were excluded if there was inadequate documentation to confirm this as the cause of death.

Autoantibody studies. All patients had an antinuclear antibody (ANA) test performed in the same laboratory using human epithelial cell line (HEp-2) cells as substrate and the ANA staining pattern was recorded. Specific antibody tests were then performed using described techniques[13,16]. Patients were divided into 3 groups: (1) anticentromere antibody-positive (ACA); (2) nucleolar staining on ANA (ANoA), with no other specific autoantibody detected such as anti-topoisomerase or anti-RNA polymerase III antibody; and (3) anti-topoisomerase I antibody-positive (TOPO). Some patients with nucleolar staining had additional tests that were positive for anti-U3-RNP, anti-Th/To, and anti-PM-Scl antibodies. We chose to look at the less specific nucleolar pattern because specific autoantibody tests for the nucleolar antibodies are generally not commercially available. Thus, our findings are designed to assist the practicing rheumatologist.

Lung subgroups. In order to determine the characteristics of lung disease in patients with the 3 different autoantibodies, we artificially divided patients into 3 subgroups of severe lung disease: (1) SPF — patients with FVC < 55% predicted; (2) PAH — patients with sPAP > 50 mm Hg on echocardiogram (who did not have a catheterization; n = 39) or a mean PAP on right heart catheterization > 25 mm Hg (n = 53); and (3) combined SPF and PAH — patients with evidence of both severe lung diseases as described above.

Clinical measures. We looked at the demographics of the different groups, disease duration at the time of diagnosis of severe lung disease, the lowest recorded FVC and diffusing capacity for carbon monoxide (DLCO)% predicted, the highest ratio of the FVC% predicted/DLCO% predicted (FVC%/DLCO%), the highest sPAP, the frequency and duration of oxygen use, and a measure of the degree of dyspnea as recorded on the patient-completed lung scale of the Scleroderma Health Assessment Questionnaire (SHAQ)[17].

Data analysis. The Pittsburgh Scleroderma Databank uses the Medlog database management system. Data analysis included descriptive statistics, means, chi-squares, Pearson's correlations, Kaplan-Meyer survival analysis, and analysis of variance.

RESULTS

A total of 833 patients had a positive ACA (n = 309), ANoA (n = 185), or TOPO (n = 339) during this time period. Figure 1 shows the frequency of severe lung disease, as defined above, in the entire patient antibody subsets. In patients with ACA, 18% had PAH, 2% had SPF, and only 0.4% had a combination of both, for a total of 20.4% with severe lung disease. Twenty-three percent of TOPO had severe lung disease; most were patients with SPF. Thirty-two percent of the ANoA group had severe lung disease ($p < 0.005$ for ANoA vs ACA or TOPO). This is particularly important since the overall frequency of nucleolar antibodies is significantly lower than either ACA or TOPO[4].

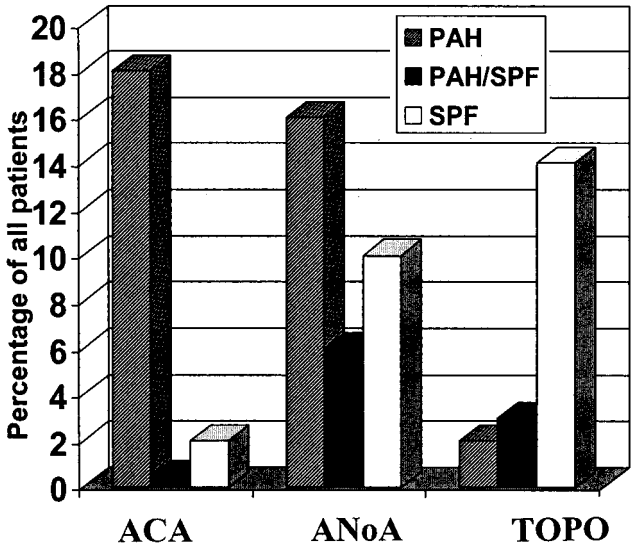

Figure 1. The frequency of severe lung disease, pulmonary arterial hypertension (PAH), severe pulmonary fibrosis (SPF), and both types of lung disease in antibody subsets in all patients.

We looked more specifically at the patients within the antibody subsets who had severe lung disease including SPF, PAH, or a combination of SPF and PAH. There were 74, 70, and 79 of these patients in ACA, ANoA, and TOPO, respectively. Eleven patients with ACA, 9 with ANoA, and 10 with TOPO had inadequate objective data to confirm the presence of severe lung disease. The final study group included 63 ACA, 61 ANoA, and 69 TOPO patients.

Table 1 shows the demographic and clinical features of the 3 autoantibody subgroups with severe lung disease. Patients with an ACA were most often Caucasian women with long-standing, limited cutaneous scleroderma. Forty-two percent of the TOPO patients were male, which is more than is seen in the entire database[4]. Both ANoA and TOPO had large percentages of African American patients (18% in ANoA and 16% in TOPO). The overall African American frequency in the Pittsburgh Scleroderma Database is 8% and thus the per-

Table 1. Demographic and clinical information on the autoantibody subsets of scleroderma patients with severe lung disease.

	ACA, n = 63	ANoA, n = 61	TOPO, n = 69
Age onset, yrs	42	42	43
Sex (% male)	4	21	42
African American, %	3	18	16
Skin score	6	13	23
Diffuse scleroderma, %	3	34	77
Disease duration at diagnosis of PAH or SPF, yrs	13.0	10.4	5.5

ACA: anticentromere antibody; ANoA: antinucleolar antibody; TOPO: antitopoisomerase I antibody; PAH: pulmonary arterial hypertension; SPF: severe pulmonary fibrosis.

centage of African Americans in both the ANoA and TOPO groups was significantly higher than expected ($p < 0.001$). Less than 2% of our population is Hispanic or Asian, so we cannot determine any meaningful information in this population. Disease duration from the first symptom attributable to scleroderma until the time of documentation of PAH or SPF was longest in the ACA group and shortest in the TOPO group.

Figure 2 shows the frequency of PAH and SPF in the patients with severe lung disease in the 3 autoantibody groups. The most frequent lung disease was "isolated" PAH, 87% in ACA patients, 47% in ANoA patients, and 10% in TOPO patients ($p < 0.001$). Severe pulmonary fibrosis was present in 6% of ACA patients, 32% of ANoA patients, and was most common in TOPO patients (72%) ($p < 0.001$). A combination of PAH with SPF occurred in only 1 ACA patient and in 20% of the ANoA patients and 18% of the TOPO patients.

The most abnormal pulmonary function tests (PFT) and sPAP for the patients in the 3 groups are shown in Table 2. The mean lowest FVC was in the TOPO group and the highest in the ACA group. Only 10% of ACA patients had a FVC < 55% predicted. The mean lowest DLCO was between 33% and 44% predicted, with the ANoA group being the lowest (nonsignificant). The mean highest FVC%/DLCO% ratio was 1.8 and 1.9 in ACA and ANoA patients, respectively, but was only 1.2 in the TOPO group ($p < 0.001$). The frequency of patients with a FVC%/DLCO% ratio > 1.6 in the ACA and ANoA groups was significantly greater than the TOPO patients. Only 7 (15%) TOPO patients had a ratio > 1.6 compared to 68% and 63% in the ACA and the ANoA ($p < 0.001$). All 223 patients in this study reported shortness of breath. The mean highest recorded scores on the lung visual analog scale of the SHAQ (range 0–3) were almost identical in the ACA, ANoA, and TOPO groups (1.64 to 1.73, on a scale of 0–3).

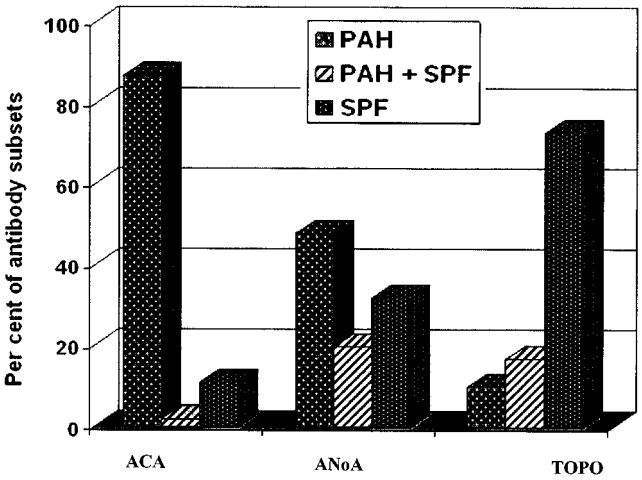

Figure 2. The frequency of pulmonary arterial hypertension (PAH), severe pulmonary fibrosis (SPF), and both types of lung disease in antibody subsets in patients with severe lung disease.

Table 3 summarizes the cardiopulmonary measures in the patients with PAH without severe pulmonary fibrosis. There were only 7 TOPO patients in this group. Although none of the patients had severe fibrosis, patients with the ANoA and TOPO antibodies had evidence of some interstitial disease with decreased FVC. The ANoA FVC was significantly lower at 71% predicted compared to the ACA patients at 81% ($p < 0.005$). The ANoA PAH patients had an even lower DLCO than the ACA PAH patients. Thus, the FVC%/DLCO% ratio was actually higher in the ANoA patients than in the ACA PAH patients (2.4 vs 1.8; $p < 0.01$). The sPAP in the ACA and ANoA patients was significantly higher than in the TOPO group, 76 and 78 mm Hg in the ACA and ANoA groups, compared to 52 mg Hg in the TOPO group ($p < 0.001$). Only one ACA and one ANoA patient had used oxygen for more than 6 months prior to the diagnosis of PAH. Even though the ANoA patients had some fibrosis the absence of significant hypoxemia prior to the diagnosis of PAH makes it most likely that a vasculopathy was the etiology of the PAH. In contrast, 5/7 of the TOPO patients required oxygen for 2–7 years before the diagnosis of PAH. Even though the TOPO patients did not have severe interstitial disease by our criteria their PH may have been secondary to chronic hypoxia. One additional difference was that 38% of the ANoA PAH patients had diffuse scleroderma. This is in direct contrast to the ACA patients, none of whom had diffuse scleroderma.

PH in the setting of severe fibrosis was present in one ACA

Table 2. Cardiopulmonary features of lung disease in autoantibody subsets.

Feature	ACA, n = 63	ANoA, n = 61	TOPO, n = 69	p
FVC % predicted	79 ± 17	56 ± 23	43 ± 13	*
DLCO % predicted	44 ± 14	33 ± 15	39 ± 14	NS
Mean ratio of FVC %/DLCO %	1.8 ± 0.5	1.9 ± 1.0	1.2 ± 0.6	**
Mean PASP, mm Hg	76 ± 17 (n = 46)	69 ± 20 (n = 41)	44 ± 15.2 (n = 47)	***
SHAQ Lung Scale	1.64 ± 0.88	1.70 ± 0.89	1.73 ± 0.91	NS

* ACA vs ANoA $p < 0.001$; ACA, ANoA vs TOPO $p < 0.001$. ** ACA, ANoA vs TOPO $p < 0.001$. *** ACA vs ANoA $p < 0.05$; ACA, ANoA vs TOPO $p < 0.001$. FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; PASP: pulmonary artery systolic pressure; SHAQ: Scleroderma Health Assessment Questionnaire. For other abbreviations see Table 1.

patient, 12 patients with ANoA, and the 12 TOPO patients (Table 4). The ANoA and TOPO patients had severe restrictive disease, with FVC 46% predicted and 41% predicted, respectively. The mean DLCO in both these groups was very low, 28% predicted in the ANoA patients and 37% predicted in the TOPO. This resulted in an increased FVC%/DLCO% ratio, 1.6, in the ANoA group compared to 1.1 in the TOPO group. The sPAP was again significantly higher in the ANoA group than the TOPO group, 78 mm Hg vs 58 mm Hg ($p < 0.05$).

Many of these patients were seen before treatment with cyclophosphamide was used for interstitial lung disease, so only 22 of them were treated. PAH drugs were generally not available for these patients. Consequently, survival, particularly in the patients with PAH or PAH in combination with SPF, was extremely poor. Less than 50% of these patients lived for 2 years. However, the TOPO patients who developed PAH had a better survival, mean 3.9 years. Patients with SPF had the best survival and only half of the TOPO patients with SPF actually died of lung disease in spite of having a FVC < 55% predicted. Twenty-six percent of the TOPO patients died of other scleroderma related causes and 23% died of non-scleroderma causes, including 3 patients who died of lung cancer.

We were able to determine autoantibody specificities for some of the ANoA patients. Twenty of the 61 had anti-U3 ribonuclear protein (RNP) and 19 had anti-Th/To antibodies. Twenty-two either did not have either of these antibodies (n = 6) or were not tested (n = 16). There were no African Americans in the Th/To group, but 42% of the U3-RNP group was African American. Similarly there were no patients with anti-Th/To who had diffuse scleroderma, whereas 74% of the U3-RNP antibodies had diffuse scleroderma (data not shown). Both groups had mixtures of lung disease. Although not statistically significant, the Th/To group more frequently had SPF alone and the U3-RNP group more frequently had PAH alone. Interestingly, Fischer and colleagues found idiopathic pulmonary fibrosis patients with anti-Th/To[18].

DISCUSSION

Since 1980, when renal crisis became a treatable complication of SSc, the primary cause of scleroderma related deaths has been lung involvement, either from pulmonary fibrosis and/or PAH[1]. These 2 pulmonary complications have very different clinical manifestations, pathophysiology, natural history, and treatment. Thus, it is extremely important to carefully evaluate each patient with SSc to determine what type of lung disease is present.

Autoantibodies have been shown to be strongly associated with specific types of lung disease[6,8]. Our study confirms that serum ACA and TOPO are closely associated with primary vasculopathy and severe fibrosis, respectively. Only 2 of 309 (< 1%) ACA-positive patients in the entire Pittsburgh Scleroderma Database have had severe pulmonary fibrosis. Severe lung disease is less common in patients with the other scleroderma-specific autoantibodies. In 132 anti-RNA polymerase III antibody patients, there were only 11 patients with severe lung disease; 8 had PAH, including 4 who had prior renal crisis[19]. In U1-RNP patients, 13 of 88 patients with this antibody had severe lung disease. Interestingly, 5 of the 9 patients with PAH had early active disease with overlap symptoms and very high PAP, and had complete resolution when they were treated with steroids.

Table 3. Cardiopulmonary features of patients with pulmonary hypertension without severe pulmonary fibrosis in autoantibody subsets.

Feature	ACA, n = 55	ANoA, n = 29	TOPO, n = 7	p
FVC % predicted	81 ± 17	71 ± 10	70 ± 13	*
DLCO % predicted	44 ± 14	30 ± 13	45 ± 14	*
Mean ratio of FVC %/DLCO %	1.8 ± 0.5	2.4 ± 1.0	1.45 ± 0.6	**
Mean sPAP, mm Hg	76 ± 17	78 ± 20	52 ± 13	***

* $p < 0.005$ ACA vs ANoA. ** $p < 0.001$ ACA vs ANoA, $p < 0.02$ ANoA vs TOPO. *** $p < 0.005$ ACA, ANoA vs TOPO. For abbreviations see Tables 1 and 2.

Table 4. Cardiopulmonary features of patients with severe pulmonary hypertension with severe pulmonary fibrosis in autoantibody subsets.

Feature	ACA, n = 1	ANoA, n = 12	TOPO, n = 12	p
FVC % predicted	53	44 ± 12	41 ± 15	NS
DLCO % predicted	23	28 ± 9	37 ± 12	*
Mean ratio of FVC %/DLCO %	2.3	1.6 ± 0.6	1.1 ± 0.5	*
Mean sPAP, mm Hg	76	76 ± 25	58 ± 9	*

* $p < 0.05$ ANoA vs TOPO. For abbreviations see Tables 1 and 2.

PH in SSc can result from a primary vasculopathy or can be secondary to severe interstitial lung disease with chronic hypoxia. Previously, PH in SSc was termed "isolated" or "vascular" PH since most of these patients had minimal or no interstitial lung disease[20]. Typically, they had longstanding limited cutaneous scleroderma, ACA, and a low DLCO. However, PH in SSc can also be secondary to severe interstitial fibrosis with chronic hypoxia, as is seen in idiopathic pulmonary fibrosis[21]. Most of our anti-TOPO patients with PH fit this description. Their mean FVC was 43% predicted and 75% had chronic hypoxia requiring oxygen supplementation for a mean of 5.2 years prior to the diagnosis of PH. Yamane, *et al* also found an increased frequency of anti-TOPO in SSc patients with secondary PH, although they used a FVC cutoff of 70% predicted to define severe fibrosis[22]. Their study did not include patients with a nucleolar ANA and they did not include the actual pulmonary pressure in their study.

Interestingly, the systolic PAP in the ACA and ANoA patients in both PAH subgroups was greater than 70 mm Hg, whereas in the TOPO PAH patients without SPF, the mean sPAP was only 52 mm Hg, and with fibrosis it was 58 mm Hg. This is similar to the milder degree of PH that is seen in patients with idiopathic pulmonary fibrosis[21]. Thus, most of the TOPO patients with PH in this study are likely secondary to hypoxic-driven PH. Consistent with this is the finding that 75% of the TOPO patients required oxygen supplementation for a mean of 4 years prior to the diagnosis of PH. This is important, since the treatment of PH secondary to severe fibrosis has not been as well studied as PAH. Although some feel that the use of an endothelin antagonist is a potential problem in patients with PH, it has been used successfully[23]. However, others feel inhaled prostacyclins may be better for these patients[24]. TOPO patients, even with PH, had a FVC%/DLCO% ratio that was significantly lower than that seen in the ACA and ANoA patients who had PAH. Thus, the duration of hypoxia, the specific scleroderma autoantibody, and the FVC%/DLCO% ratio may all be important clues to the type of PH that the patient has.

Our study suggests that there are patients with ANoA who have moderate to severe interstitial fibrosis and yet develop severe PAH without prior chronic hypoxia. They have levels of pulmonary arterial pressures that are "out of proportion" to the degree of fibrosis. These ANoA patients had a significantly lower FVC than was seen in the ACA patients with PAH. However, they also had a marked increased FVC%/DLCO% ratio with a very low DLCO. They did not have chronic hypoxia prior to diagnosis of PAH and their sPAP and survival were similar to the ACA patients with PAH, suggesting that they had a primary vasculopathy along with some fibrosis. Thus, patients with a ANoA and severe lung disease have a high likelihood of having a significant vasculopathy with PAH even if they have significant interstitial fibrosis. Knowing these features will help physicians be better able to diagnose and treat these complicated patients. This is important since many of the ANoA patients had diffuse scleroderma and were African American, features that are not usually seen in the more typical vasculopathic PAH in ACA patients.

Anti-U3-RNP and anti Th/To antibodies are the most common antinucleolar antibodies. Since commercial methods for detecting these antibodies are not readily available, a surrogate may be a nucleolar staining pattern on routine ANA testing using immunofluorescence. ELISA for determining ANA do not identify the staining patterns and do not contain these 2 antigens, so the ELISA ANA in these patients are often negative. It is very important to insist on having an ANA performed using an immunofluorescence method so the staining pattern can be identified.

Until recently there has been no effective treatment for PAH. Therefore, making this diagnosis did not change the overall treatment plan. Since therapy for PAH has been available in the last 8 years, patients with SSc are being more carefully evaluated for evidence of PAH. Also, with the use of high resolution CT scans, it is clear that PAH is seldom seen in the complete absence of interstitial lung disease. This has made it more difficult to determine whether the patient's problem is primarily from the pulmonary fibrosis, hypoxia-driven PH, or vascular PAH.

There are many limitations in the interpretation of these data. The largest problem just deals with observational data and the lack of uniform followup of the patients. Many patients did not have complete data. While initial echocardiograms have been standard in our practice, patients did not often have followup echocardiograms once the diagnosis of PAH was made, so the highest levels of pressures were not known. Many of the patients had multiple PFT, which change with time. We tried to use the ones closest to the diagnosis of PAH, but they were not always simultaneous. However, we think the numbers of the patients and the relative consistency of these findings will help physicians to better understand these patients and the complicated lung disease in scleroderma.

Our study shows that there are major differences in the lung disease associated with the different autoantibodies. We know that these autoantibodies are associated with different specific genetic markers[25]. Recognizing these differences is important to better understand the basic pathogenic and genetic mechanisms of scleroderma. ACA and TOPO are strongly associated with PAH and SPF and we have shown that the patients with a nucleolar antibody also have a unique type of lung disease. These differences suggest that the different autoantibodies may actually represent different diseases with different pathogenesis.

Serum autoantibodies in combination with the ratio of the FVC%/DLCO% are helpful in determining whether the dominant pulmonary physiologic process is a vasculopathy or interstitial lung disease. The differences in treatment for progressive pulmonary fibrosis, secondary hypoxic-driven PH, and vascular PAH are all very different. These findings are clues as to the type of lung disease the patient has and should be helpful in determining the best approach to therapy.

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