Pulmonary & Respiratory Medicine

Ferreira et al., J Pulmonar Respirat Med 2012, 2:1
http://dx.doi.org/10.4172/2161-105X.1000116

Case Report Open Access

Are Anti-Ro52 Antibodies Associated with Pulmonary Involvement in Scleroderma?

Joao Pedro Ferreira[1]*, Isabel Almeida[1,2], Antonio Marinho[1,2], Conceicao Cerveira[1,2] and Carlos Vasconcelos[1,2]

[1]*Unidade de Imunologia Clínica, Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal*
[2]*Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), UMIB, Universidade do Porto, Porto, Portugal*

Abstract

Introduction: The presence of anti-Ro52 antibodies has been reported in a wide variety of autoimmune diseases, particularly in myositis, scleroderma and autoimmune liver diseases. Clinical significance of anti-Ro52 antibodies remains controversial. Studies are lacking in clarifying the association of anti-Ro52 with pulmonary involvement in scleroderma.

Objectives: To determine if anti-Ro52 antibodies are associated with pulmonary involvement (interstitial, indirect pulmonary hypertension, or both) in scleroderma.

Methods: Single center, retrospective study based on immunoblotting panel analysis and patients clinical records.

Pulmonary manifestations were sub-grouped in: 1) interstitial (alveolitis and/or fibrosis), 2) pulmonary artery systolic pressure (PASP) ≥40 mmHg plus interstitial pulmonary disease, and 3) isolated PASP≥40 mmHg (purely vascular).

Results: Our scleroderma cohort included 200 patients, of which 137 had immunoblotting panels with anti-Ro52 reactivity analysis. The search was conducted between January 2010 and July 2011.

The frequency of pulmonary manifestations in patients with positive anti-Ro52 antibodies was 67.7% (n=31), and 60% (n=24) in the negative anti-Ro52 group, showing no significant differences between groups (p=0.621).

Still no significant differences were found when pulmonary manifestations were evaluated according to the subgroups (p=0.525).

Sensitivity, specificity, positive and negative predictive values of anti-Ro52 reactivity for determining pulmonary involvement in scleroderma were low.

Conclusion: No association was found between positive anti-Ro52 antibodies and pulmonary involvement in scleroderma.

Keywords: Anti-Ro52 antibodies; Pulmonary involvement; Scleroderma

Introduction

Antibodies to SSA antigen (Ro52/Ro60), were historically described as a marker for Sjögren syndrome and systemic lupus erythematosus [1]. However, recent publications [2,3] have demonstrated that Ro52 and Ro60 (SSA) antigens consisted of two different proteins representing two distinct autoantibodies systems and have different clinical associations. In clinical practice is desirable to detect these autoantibodies separately [4].

The Ro52 gene has been mapped to the end of the short arm of human chromosome 11 [5] and Ro52 antigen has recently been identified as a 52 kDa protein, belonging to the tripartite motif (TRIM) protein family [6]. So, anti-Ro52 antibodies can also be named as anti-TRIM21 antibodies.

Clinical significance of anti-Ro52/TRIM21 antibodies remains controversial [7,8].

The presence of anti-Ro52 antibodies has been reported in a wide variety of autoimmune diseases, particularly in myositis, scleroderma and autoimmune liver diseases [9,10], and have been associated with non-autoimmune diseases such as viral infections or neoplastic diseases [11].

Some studies found association between anti-Ro52 reactivity and scleroderma [12]. Others described association between anti-Ro52 reactivity and interstitial lung disease [7]. No association between anti-Ro52 antibodies, scleroderma and interstitial lung disease altogether was found in the reviewed literature.

The scarce information about this issue has led to the development of this study.

Objectives

To determine if anti-Ro52 antibodies are associated with pulmonary manifestations in scleroderma.

Methods

Studied population

In this single center, retrospective study, the patients were selected on the basis of immunoblotting panels (EUROLINE®) results and patients clinical records.

Inclusion criteria

Patients followed in our center with scleroderma diagnosis criteria

***Corresponding author:** Joao Pedro Ferreira, Unidade de Imunologia Clínica, Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal, E-mail: jp7ferreira@hotmail.com

Received January 04, 2012; **Accepted** March 13, 2012; **Published** March 15, 2012

Citation: Ferreira JP, Almeida I, Marinho A, Cerveira C, Vasconcelos C (2012) Are Anti-Ro52 Antibodies Associated with Pulmonary Involvement in Scleroderma?. J Pulmonar Respirat Med 2:116. doi:10.4172/2161-105X.100011

[13], which had a pulmonary computed tomography (CT) scan and an echocardiogram performed.

Definitions

Pulmonary manifestations were sub-grouped in: 1) interstitial (alveolitis and/or fibrosis), 2) pulmonary artery systolic pressure (PASP) ≥40 mmHg plus interstitial pulmonary disease, and 3) isolated PASP≥40 mmHg (purely vascular) [14].

Interstitial pulmonary involvement was determined by radiologist interpretation of high-resolution CT scan (HRCT) and/or bronchoalveolar lavage results.

Doppler study is the most accurate non-invasive measure of PASP with a sensitivity of 90% and a specificity of 75% compared with right heart catheterization [15]. An important point of discussion is the definition of the cut-off value to distinguish normal from abnormal PASP. Some authors consider normal an estimated PASP lower than 30 mmHg [14]. In our center we consider a PASP ≥40 mmHg highly suggestive of pulmonary arterial hypertension (PAH) and a potential indication for right heart catheterisation. For this study purposes we assume that patients with PASP ≥40 mmHg are likely to have elevated pulmonary artery pressure.

Data analysis

Data were registered in Excel® and IBM SPSS software version 19® was used for statistical analysis. For proportion analysis chi-square or Fisher tests were used. A significance (p) < 0,05 was defined. Complementary information in data analysis is mentioned along the text and tables.

Results

Our scleroderma cohort included 200 patients, of which 137 had immunoblotting panels with anti-Ro52 reactivity analysis. The search was conducted between January 2010 and July 2011.

Of the 137 patients with anti-Ro52 reactivity analysis, 71 (51.8%) had inclusion criteria: 93% (n=66) were women and 7% (n=5) were men, with a mean (SD) age of 56.4 (14.5) years.

Among the 71 selected sera, 43.7% (n=31) had anti-Ro52 reactivity. Among the 31 positive sera, 22.6% (n=7) showed isolated anti-Ro52 antibodies and 77.4% (n=24) showed anti-Ro52 antibodies associated with at least another antibody.

The gender distribution and mean age (SD) of the positive anti-Ro52 group were similar to the initial group (96.8% women; 54.6 (13.7) years, respectively).

Altogether the frequency of pulmonary manifestations in the positive anti-Ro52 antibodies was 67.7% (n=31), and 60% (n=24) in the negative anti-Ro52 group. No significant differences between groups were found (p=0.621).

Pulmonary manifestations were also evaluated according to the subgroups-1) interstitial (alveolitis and/or fibrosis), 2) PASP≥40 mmHg plus interstitial pulmonary disease, and 3) isolated PASP ≥40 mmHg (purely vascular). Still no significant differences were found (Table 1).

	Anti-Ro52 antibody		
Pulmonary involvement	Positive n (%)	Negative n (%)	p
Isolated Interstitial (alveolitis and/or fibrosis)	20 (64.5%)	21 (52.5%)	0.525*
PASP ≥40 plus Interstitial	1 (3.1%)	3 (7.5%)	0.525*
Isolated PASP ≥40 (purely vascular)	4 (12.9%)	8 (20%)	0.322*

Table 1: Pulmonary involvement in relation to anti-Ro52
PASP, pulmonary artery systolic pressure (mmHg)
*Chi-square test

		($CI_{95\%}$)			
IPI	PARo52A	Ss, %	Sp, %	PPV, %	NPV, %
n=41	n=20	48.7 (29-71)	44.4 (20-68)	66.7 (46-88)	43.2 (19-67)

Table 2: Sensitivity (Ss), specificity (Sp), positive (PPV) and negative (NPV) predictive values of anti-Ro52 reactivity in determining pulmonary involvement in scleroderma
IPI, interstitial pulmonary involvement; PARo52A, positive anti-Ro52 antibodies.

Calculations for sensitivity (48.7%), specificity (44.4%), positive (66.7%) and negative (43.2%) predictive values of anti-Ro52 reactivity for determining interstitial pulmonary involvement in scleroderma are detailed in Table 2.

Among patients with interstitial pulmonary involvement (n=41), 39% (n=16) had positive anti-Scl70 antibodies. In the group of patients without interstitial pulmonary involvement (n=26), only 7.7% (n=2) had positive anti-Scl70 antibodies. Significant differences between groups were found (p=0,005).

Among patients with interstitial pulmonary involvement (n=41), 53.7% (n=22) had positive anti-centromere antibodies. In the group of patients without interstitial pulmonary involvement (n=26), 76.9% (n=20) had positive anti-centromere antibodies. No significant differences between groups were found (p=0,06). All patients (n=4) with isolated PASP ≥40 mmHg (purely vascular) had positive anti-centromere antibodies.

Anti-Ro52 antibodies were not associated with anti-Scl70, nor anti-centromere antibodies (p=0,116 and p=0,646, respectively).

Discussion

Isolated anti-Ro52 antibodies were detected in various autoimmune diseases. Some authors describe an association between anti-Ro52 antibodies and interstitial lung disease [7].

Some studies report an association of anti-Ro52 antibodies with aggressive anti-tRNA synthetases syndrome [16,17]. However, there have been relatively few studies addressing the frequency of anti-Ro52 antibodies in scleroderma and no comprehensive reports assessing associations of anti-Ro-52 with the specific autoantibodies that are characteristic of scleroderma [12]. In addition, after extensive *MEDLINE/PubMed* review, we did not find studies reporting an association of anti-Ro52 with pulmonary involvement in scleroderma.

In a large study [12] the authors analysed sera from a substantial cohort of scleroderma patients representing the entire spectrum of disease. Anti-Ro52 was found to be present at a frequency of at least 15% in all antibody groups tested. This frequency appeared to be greater than previously described [18,19]. The data presented in this study demonstrate that anti-Ro52 is prevalent throughout the scleroderma supporting the hypothesis that anti-Ro52 is a general serum marker with limited linkage to a myositis phenotype or other clinical manifestations of scleroderma.

In our study the prevalence of anti-Ro52 antibodies was even greater than previously described [12,18,19] reaching 43.7% of the tested sera. The data presented in our study demonstrate that anti-Ro52 antibodies lack sensitivity, specificity and predictive values for pulmonary involvement diagnosis in scleroderma. In addition, no independent association was found between anti-Ro52 reactivity and pulmonary disease even when pulmonary manifestations where subgrouped in

interstitial (alveolitis and/or fibrosis), PASP≥40 mmHg plus interstitial pulmonary disease, and isolated PASP ≥40 mmHg (purely vascular). These findings are supported by previous studies [12].

Our study has several limitations: it is a short cross-sectional study; the diffusion capacity for carbon monoxide was not addressed; the lung CT scores were not performed; echocardiography has important limitations for diagnosing PASP elevation etiology [20-23].

In fact, our study confirmed some associations previously described: anti-Scl70 antibodies with interstitial pulmonary disease and anti-centromere antibodies with potential vascular pulmonary hypertension [24-26].

Conclusion

No association was found between positive anti-Ro52 antibodies and pulmonary involvement in scleroderma.

References

1. Schulte-Pelkum J, Fritzler M, Mahler M (2009) Latest update on the Ro/SS-A autoantibody system. Autoimmun Rev 8: 632-637.
2. Ben Chetrit E, Chan EK, Sullivan KF, Tan EM (1988) A 52-KD protein is a novel component of the SS-a/Ro antigenic particle. J Exp Med 167: 1560-1571.
3. Chan EK, Harnel JC, Buyon JP, Tan EM (1991) Molecular definition and sequence motifs of the 52-kD component of human SS-A/Ro autoantigen. J Clin Invest 87: 68-76.
4. Defendenti C, Atzeni F, Spina MF, Grosso S, Cereda A, et al. (2011) Clinical and laboratory aspects of Ro/SSA52 autoantibodies. Autoimmun Rev 10: 150-154.
5. Frank MB, Itoh K, Fujisaku A, Pontarotti P, Mattei MJ, et al. (1993) The mapping of the human 52 kDa Ro/SSA autoantigen gene to human chromossome 11. Am J Hum Genet 52: 183-191.
6. Rhodes DA, Ihrke G, Reinicke AT, Malchrek G, Towey M, et al. (2002) The 52000 MW Ro/SS-A autoantigen in Sjögren syndrome/systemic lupus erythematosus (Ro52) is an interferon gamma inducible tripartite motif protein associated with membrane proximal structures. Immunology 106: 246-256.
7. Ghillani P, André C, Toly C, Rouquette AM, Bengoufa D, et al. (2011) Clinical significance of anti Ro-52 (TRIM21) antibodies with anti-SSA 60 kDa antibodies: Results of a multicentric study. Autoimmun Rev 10: 509-513.
8. Rhodes DA, Trowsdale J (2007) TRIM21 is a trimeric protein that binds IgG Fc via the B30.2 domain. Mol Immunol 44: 2406-2414.
9. Rutjes SA, Vree Egberts WT, Jongen P, Van Den Hoogen F, Pruijn GJ, et al. (1997) Anti Ro52 antibodies frequently co-occur with anti Jo-1 antibodies in sera from patients with idiopathic inflammatory myopathy. Clin Exp Immunol 109: 32-40.
10. Granito A, Muratori P, Muratori L, Pappas G, Cassani F, et al. (2007) Antibodies to SSA/Ro52 and centromere in autoimmune liver disease: a clue to diagnosis and prognosis of primary biliary cirrhosis. Aliment Pharmacol Ther 26: 831-838.
11. Hervier B, Rimbert M, Colonna F, Hamidou MA, Andrain M (2009) Clinical significance of anti-Ro/SSA-52 kDa antibodies : a retrospective monocentric study. Rheumatology 48: 964-967.
12. Parker JC, Burlingame RW, Bunn CC (2009) Prevalence of antibodies to Ro52 in a serologically defined population of patients with systemic sclerosis. J Autoimmune Dis 6: 2.
13. (1980) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 23: 581-590.
14. Mattucci-Cerinic M, D`Angelo S, Denton CP, Vlachoyiannopoulus P, Silver R (2003) Assessment of lung involvement. Clin Exp Rheumatol 21: S19-S23.
15. Denton CP, Cailes JB, Phillips GD, Wells AU, Black CM, et al. (1997) Comparison of doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. Br J Rheumatol 36: 239-243.
16. La Corte R, La Mo Naco A, Lacaputo A, Dolzani F, Trotta F (2006) In patients with antisynthetase syndrome the occurence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease. Autoimmunity 39: 249-253.
17. Sibilia J, Chatelus E, Meyer A, Gottenberg JE, Sordet C, et al. (2010) How can we diagnose and better understand inflammatory myopathies? The usefulness of auto-antibodies. Presse Med 39: 1010-1025.
18. Frank MB, McCubbin V, Trieu E, Wu Y, Isenberg DA, et al. (1999) The association of anti-Ro52 autoantibodies with myositis and scleroderma autoantibodies. J Autoimmun 12: 137-142.
19. Fujimoto M, Shimozuma M, Yazawa N, Kubo M, Ihn H, et al. (1997) Prevalence and clinical relevance of 52-kDa and 60-kDa Ro/SS-A autoantibodies in Japanese patients with systemic sclerosis. Ann Rheum Dis 56: 667-670.
20. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et al. (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 34: 1219-1263.
21. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, et al. (2004) Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43: 5S-12S.
22. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, et al. (2009) Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 179: 151-157.
23. Vonk Noordegraaf A, Naeije R (2008) Right Ventricular Function in Scleroderma-Related Pulmonary Hypertension. Rheumatology 47: v42-v43.
24. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, et al. (2007) Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 66: 754-763.
25. Hu PQ, Fertig N, Medsger TA Jr, Wright TM (2003) Correlation of serum anti-DNA topoisomerase I antibody levels with disease severity and activity in systemic sclerosis. Arthritis Rheum 48: 1363-1373.
26. Russo K, Hoch S, Dima C, Varga J, Teodorescu M (2000) Circulating anticentromere CENP-A and CENP-B antibodies in patients with diffuse and limited systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. J Rheumatol 27: 142-148.
27. Steen VD (2005) Autoantibodies in Systemic Sclerosis. Semin Arthritis Rheum 35: 35-42.