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Significance of Anti-Centromere Antibodies

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Abstract

Anti centromere antibodies (ACA) are a specific pattern of antinuclear antibodies (ANA). There are many autoimmune and systemic diseases associated with anticentromere antibodies (ACA). In fact, ACA are part of the denominated systemic sclerosis (SSc)-specific autoantibody. However, some studies and clinical practice have reported the existence of positive ACA in the general population without associated autoimmune disease associated. Also, it has been described an increased risk of malignancy has been described among patients diagnosed with systemic sclerosis (SSc). Different authors have demonstrated that ANAs are presented, not only in autoimmune diseases, but also in the serum of patients with different types of cancer. Thus, this fact has been previously studied in patients with LES focused on a subset of lupus autoantibodies that penetrate cells. The autoantibodies can inhibit DNA repair or directly damage DNA, leading to the accumulation of DNA damage which increases the risk of cancer in these patients. The present study is performed in a teaching hospital in Santiago de Compostela. Demographic, clinical, capillaroscopic and immunological characteristics and complementary tests were analysed. A total of 236 patients were involved. Overall, 90.3 % were female with a mean age of 64.0 years old (range = 22-92 years). We detected autoimmune diseases in 140 patients (59.3%). The most frequent was Systemic Sclerosis (55.9%), followed by primary biliary cirrhosis (9.3%), primary Sjögren's syndrome (7.2%) and autoimmune hepatitis (4.7%). Thirty-one patients reported having cancer at some point (13.1%), with three of them reporting two types of cancer. The variables associated with mortality were age, diabetes mellitus, dysphagia, anemia and the presence of pulmonary arterial hypertension. The variables associated with the diagnosis of cancer were age, alcohol consumption, monoclonal peak, chronic gastritis, interstitial lung disease, anti-DNA antibodies and anti-Jo-1 antibodies. The mortality in our cohort was 6.4%. In this review, we are going to describe all of the reported data regarding the diagnosis of autoimmune diseases and the presence of cancer in samples from patients with

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positive ACA as well as the potential factors associated with mortality in these patients. These results provide new insights into the prognosis and outcomes of these patients, but further investigations into factors that determine the risk of cancer in patients with positive ACA may be warranted.

Keywords: autoimmune, anticentromere antibodies, malignancy, Systemic sclerosis

1. Introduction

Anti centromere antibodies (ACA) are a specific pattern of antinuclear antibodies (ANA). ANA are immunoglobulin directed against autologous cell nuclear and cytoplasmic components. In the laboratory, ANA are detected with an indirect immunofluorescence (IIF) test by using the human cell line HEp-2 as a substrate. With this assay, it is possible to determine two important facts: the titre of the antibodies (refers to the highest dilution of serum that produces visible fluorescence) and the ANA pattern, which correlates to the distribution of staining produced by autoantibodies reacting with antigens in the HEp-2 cell nucleus and cytoplasm(Cabiedes and Núñez-Álvarez 2010)(Anon n.d.).

There are many autoimmune and systemic diseases associated with anticentromere antibodies (ACA). In fact, ACA are some of the denominated systemic sclerosis (SSc)-specific autoantibodies (also including anti-topo I, anti-Th/To, or anti-RNAP III)(Hudson and Fritzler n.d.). Thus, ACA are present in patients with limited SSc(Simeón-Aznar et al. 2015) (related with calcinosis and pulmonary hypertension), primary biliary cirrhosis (PBC; related to a worse outcome), systemic lupus erythematosus (SLE), Sjögren's syndrome or isolated Raynaud phenomenon(Baldini et al. n.d.)(Lee et al. 2015)(Himoto et al. 2010).

However, some studies and clinical practice have reported the existence or positive ACA in the general population without an associated autoimmune disease(Case n.d.)(Lee, Tsay, and Tsai 1993). The role that this fact can represent for the prognosis or their association with other pathologies are not well known(Zuber, Gotzen, and Filler 1994). Thus, the consequences of ACA in the general population are not well known, including the association between ACA and cancer. The association between the absence of ACA and the poor prognosis in SSc has been described since the presence of ACA is associated with cutaneous forms without systemic involvement(Skare et al. n.d.)(Ho and Reveille 2003)(Simeón-Aznar et al. 2015)(Anon n.d.). Also, an increased risk of malignancy has been described among patients diagnosed with systemic sclerosis (SSc). Also, ANAs have been associated with paraneoplastic syndromes(Kiers, Altermatt, and Lennon 1991)(Inuzuka 2000). In fact, PM/Scl antibodies seem to be associated with a higher risk of cancer with scleroderma, but there are no data concerning ACA(Bernal-Bello et al. 2017). It is essential to consider the clinical characteristics of these patients because of the potential poor prognosis. The role that ACA may play in predisposition to malignancy development and not well known.

The aim of this study is to describe the clinical manifestations and diseases associated with anticentromere antibodies, such as whwther the evaluation of these patients is concluded by

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physicians. Furthermore, an objective of this study is to investigate whether there is an increased risk of malignancy among patients with ACA.

2. Results

During the study period, a total of 236 patients were involved. Overall, 90.3 % were female with a mean age of 64.0 years old (range = 22-92 years). The mean follow up was 68.3 months. All patient histories were reviewed. In total, 97.% (229 patients) had an ACA titre of 1/320 or above. Regarding the department in which they were studied, the most frequent was rheumatology (50.8%) following by internal medicine (30.3%).

With particular focus on autoimmune disease, we detected this in 140 patients (59.3%). The most frequent pathology was SSc (55.9%), followed by primary biliary cirrhosis (9.3%), primary Sjögren's syndrome (7.2%) and autoimmune hepatitis (4.7%). Other autoimmune diseases, including polyarthritis, systemic lupus erythematosus, Raynaud phenomenon, sarcoidosis, mixed connective tissue disease, etc. were less frequent. In addition, 7.6% of cases were overlaps forms. All clinical and epidemiological characteristics are shown in Table 1.

Autoimmune diseases were not determined in 104 patients (40.7%). We reviewed the accurate diagnosis in these cases. With respect to clinical features, Raynaud phenomenon was only questioned in 55.5% and symptoms of Sjögren's syndrome in 13.2%. Physicians did not question about dysphagia in 66.1% of patients or symptoms of gastro-oesophageal reflux disease in 57.2%.

Regarding complementary tests, anti-mitochondrial antibodies (AMA) were not determined in 62.7%. Capillaroscopy was performed in 68 patients (28.2%), computed tomography of the chest in 32.2% and transthoracic echocardiography in 56.8%. Furthermore, spirometry was realized in 109 patients (46.2%), upper endoscopy in 65 patients (27.5%) and barium swallow in 40 patients (16.9%). All of the complementary tests used are shown in Table 2.

Thirty-one patients reported having had cancer at some time (13.1%), with three of them reporting two types of cancer. The most frequent were breast in 8 (25.7%), haematological malignancy in 4 (12.5%), digestive malignancy in 4 (12.5), gynaecologic malignancy in 3 (9.7%) and malignancy of unknown origin in 3 (9.7%). Cancer preceded the diagnosis of ACA in 13 patients (41.9%), with a mean time to diagnosis of 7 years (range 1-18). In 5 patients the diagnosis of autoimmune disease and malignancy was synchronous. The mortality in our cohort was 6.4% (15 patients).

The results of the univariate analysis were as follows. The variables associated with mortality were age ($p = 0.000$), diabetes mellitus ($p = 0.045$), dysphagia ($p = 0.035$), anaemia ($p = 0.005$) and the presence of pulmonary arterial hypertension ($p = 0.000$). The variables associated with the diagnosis of cancer were age ($p = 0.048$), alcohol consumption ($p = 0.009$), monoclonal peak ($p = 0.028$), chronic gastritis ($p = 0.001$), interstitial lung disease ($p = 0.000$), anti-DNA antibodies ($p = 0.032$) and anti-Jo-1 antibodies ($p = 0.028$). Lastly, the variables associated with the diagnosis of systemic sclerosis were alcohol consumption ($p = 0.024$), tobacco consumption

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(p = 0.005), anti-DNA antibodies (p = 0.000), anti-Jo-1 antibodies (p = 0.001), anti-La antibodies (p = 0.000) and anti-Scl-70 antibodies (p = 0.000). There were no significant differences in subgroup analysis between patients of different genders when comparing hospital mortality or the diagnosis of cancer.

After reviewing widely, the clinical and analytical characteristics and complementary tests of patients without autoimmune disease diagnosis, we concluded that 40.6% of cases without diagnosis might have an autoimmune disease and 15.7% could have overlap forms.

3. Discussion

Our study describes the main characteristics of a cohort of patients with positive ACA. As mentioned in the introduction, autoimmune diseases are caused by the adaptive autoimmune response. Detecting autoantibodies is a useful instrument in the diagnosis of these diseases(Anon n.d.). However, the antibodies are not always associated with the pathology and healthier populations often have circulating antibodies without the disease. ANA are immunoglobulins directed against autologous cell nuclear and cytoplasmic components. Anti centromere antibodies (ACA) are a specific type of ANA(Solomon et al. 2002).

As mentioned above, autoantibodies can be present in autoimmune diseases as well as in healthier individuals. In our series, we detected autoimmune diseases in 140 patients (59.3%)(Anon n.d.). Similar to the other studies, the most frequently diagnosed pathology was SSc (55.9%) followed by primary biliary cirrhosis (9.3%)(Skare et al. n.d.)(Chalifoux et al. 2017)(Nakamura et al. 2007). With regard to the subset of SSc, lSSc was the most frequent (79.0%), as in previous reports(Simeón-Aznar et al. 2015). The association of ACA with limited cutaneous involvement and isolated pulmonary hypertension is well known, which also means that ACA are predictors of a favourable prognosis(Hamaguchi 2010). However, these antibodies are not specific to SSc, and then had been described in other conditions such as Sjögren's syndrome (Lee et al. 2015). In our cohort, other autoimmune diseases, including polyarthritis, systemic lupus erythematosus, Raynaud phenomenon, sarcoidosis and mixed connective tissue disease, were less frequent and the 7.6% of cases were overlap forms. As in the literature regarding other autoimmune diseases, most patients were female (90.3%).

Autoimmune diseases were not concluded in 40.7%. However, after widely reviewing the clinical and analytical characteristics and complementary tests of patients without an autoimmune disease diagnosis, we concluded that 40.6% of cases without diagnosis might have an autoimmune disease and 15.7% may have overlap forms. In fact, deficits have been observed in the clinical history (for example, Raynaud, symptoms of Sjögren's syndrome or dysphagia). This makes it clear that a suboptimal method clinical history was performed, and tthere is needed to proactively investigate the symptoms associated with autoimmune disease in these patients.

On the other hand, we have also found limitations regarding complementary explorations such as anti-mitochondrial antibodies, computed tomography of the chest or spirometry. This enables us to see that conditions associated with ACA often are not suspected with the consequent under-diagnosis.

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Furthermore, studies have focused in an increased risk of malignancy among patients diagnosed with SSc. Thus, Bernal-Bello et *al*. found that PM/Scl antibodies seem to be associated with a higher risk of cancer in scleroderma(Bernal-Bello et al. 2017). However, there are few reports in the current literature focused on the risk of cancer associated with ACA(Vlagea et al. 2018)(Zuber et al. 1994)(Briasoulis et al. 2008). In this regard, in our cohort, the prevalence of cancer was 13.1%. In 3 of the patients, there were 2 types of cancer. With regard to aetiology, the most frequent was breast in 25,7% of cases, as in the study mentioned above. The next most frequent were haematological malignancy, digestive malignancy, gyneacologic malignancy and malignancy of unknown origin. It is important to bear in mind that cancer may sometimes precede the autoimmune disease; according to the results of our study, there is a mean time to diagnosis of 7 years. In a few cases, the diagnosis of autoimmune disease and malignancy was synchronous. The mechanisms for this association remain unclear, but many tumors express antigens that can induce immune responses in some patients(Daniels et al. 2005).

As mentioned in the results, we found that the variables associated with the diagnosis of cancer were age, alcohol consumption, the presence of monoclonal peak, chronic gastritis, interstitial lung disease, anti-DNA antibodies and anti-Jo-1 antibodies. In line with this, there are previous studies of other autoimmune diseases such as LES. Previous studies focused on a subset of lupus autoantibodies that penetrate cells and inhibit DNA repair or directly damage DNA, leading to the accumulation of DNA damage, which increases the risk of cancer in these patients(Noble et al. 2016). In this way, our study is one of the investigations focussing on cancer risk in patients with an ACA pattern. However, this correlation needs to be further investigated.

The mortality in our cohort was 6.4%, with the associated factors being mortality, diabetes mellitus, dysphagia, anemia, the presence of pulmonary arterial hypertension and age. Longitudinal studies with repeated assessments are needed to understand the temporal relationship between ACA, mortality and cancer.

The main limitation of this study is the retrospective condition of the analysis, which could compromise the accuracy of some clinical data inclusion. On the other hand, this study has important strengths. We have analysed not only the established diagnosis of autoimmune disease, but we also reviewed all clinical, capillaroscopic and immunological characteristics, such as complementary tests to identify individuals that can potentially can suffer an autoimmune disease, for a re-evaluation.

4. Conclusions

The ACA test is one of the most important laboratory tests in patients with suspected autoimmune disease, especially SSc. Despite this, it is very important to take into account clinical manifestations, in combination with laboratory tests, for an adequate diagnosis. Physicians must have a high suspicion of disease. Also, we should always keep in mind that it is necessary a good clinical history is necessary to guide our diagnosis and complementary tests. Our data suggest that a positive result for ACA does not always indicate the presence of a

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connective tissue disease, but an adequate clinical history is necessary to achieve an accurate diagnosis. Also, we cannot ignore the higher risk of malignancy in patients with ACA. However, this correlation needs to be further investigated. Longitudinal studies with repeated assessments are needed to understand the temporal relationship between ACA, mortality and cancer. These results provide new insights into the prognosis and outcomes in these patients, but further searches for factors that determine the risk of cancer in patients with positive ACA may be warranted.

5. Material and methods

2.1 Study population

The present study is a multicentre study performed in 3 hospitals in Galicia (Spain). This study was undertaken retrospectively. We performed a search of our electronic medical record database for all patients with one or ANA with an ACA pattern from January 2011 to 31 December 2015. All hospitals included a specific Systemic and Autoimmune Diseases Unit.

We performed a search of our electronic medical record database by reviewing their medical history. From the medical charts, we collected demographic and clinical characteristics, including comorbidities, clinical presentations, laboratory data and complementary tests. We also reviewed the diagnosis accuracy and the possibility of an alternative diagnosis.

Positive ACA determination was defined by a titre of 1/160 or higher. The possibility of autoimmune disease was defined after a systematic revision of clinical characteristics, analysis and complementary tests in those patients without an uncertain or unsuspected diagnosis.

2.2 Statistical analysis

A descriptive analysis was performed, by calculating qualitative variables rates and the mean and standard deviation of quantitative variables. We used the Chi-square test or Fisher's exact test as appropriate (expected frequency value < 5) to compare qualitative variables and Student´s t test for quantitative variables. A *P*-value < 0.05 was regarded as significant. All these analyses were performed using SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA).

2.3 Laboratory determinations

All the laboratory determinations were performed using standard commercially available methods according to the protocol of the manufacturer.

ANA were detected using an indirect immunofluorescence on HEp-2 cells (Bio-Rad Laboratories, Redmond, USA). The Hep-2 cell line is derived from a human epithelial cell tumor and yields a better sensitivity for the detection of nuclear antigens present during cell division, (for example centromere antigen), than the use of tissue sections of murine liver or kidney. ACA were detected by their characteristic staining pattern: discrete coarse speckles scattered in interphase cells and aligned at the chromatin mass on mitotic cells(Solomon et al. 2002). (fig1)

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2.4 Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki(Anon n.d.) and in full conformity with prevailing regulations. Vulnerable populations were not be participating in this study and no economic compensation was given to patients for their participation. The investigators were free to publish the results of this study, regardless of the results obtained.

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List of abbreviations:

SSc: systemic sclerosis

ACA: anticentromere antibodies

ANA: antinuclear antibodies

AMA: antimitochondrial antibodies

IIF: indirect immunofluorescence

SLE: systemic lupus erythematosus

PBC: primary biliary cirrhosis

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Author Contributions

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Figure 1. Antinuclear Antibodies (ANA) detected using an indirect immunofluorescence on HEp-2 cells

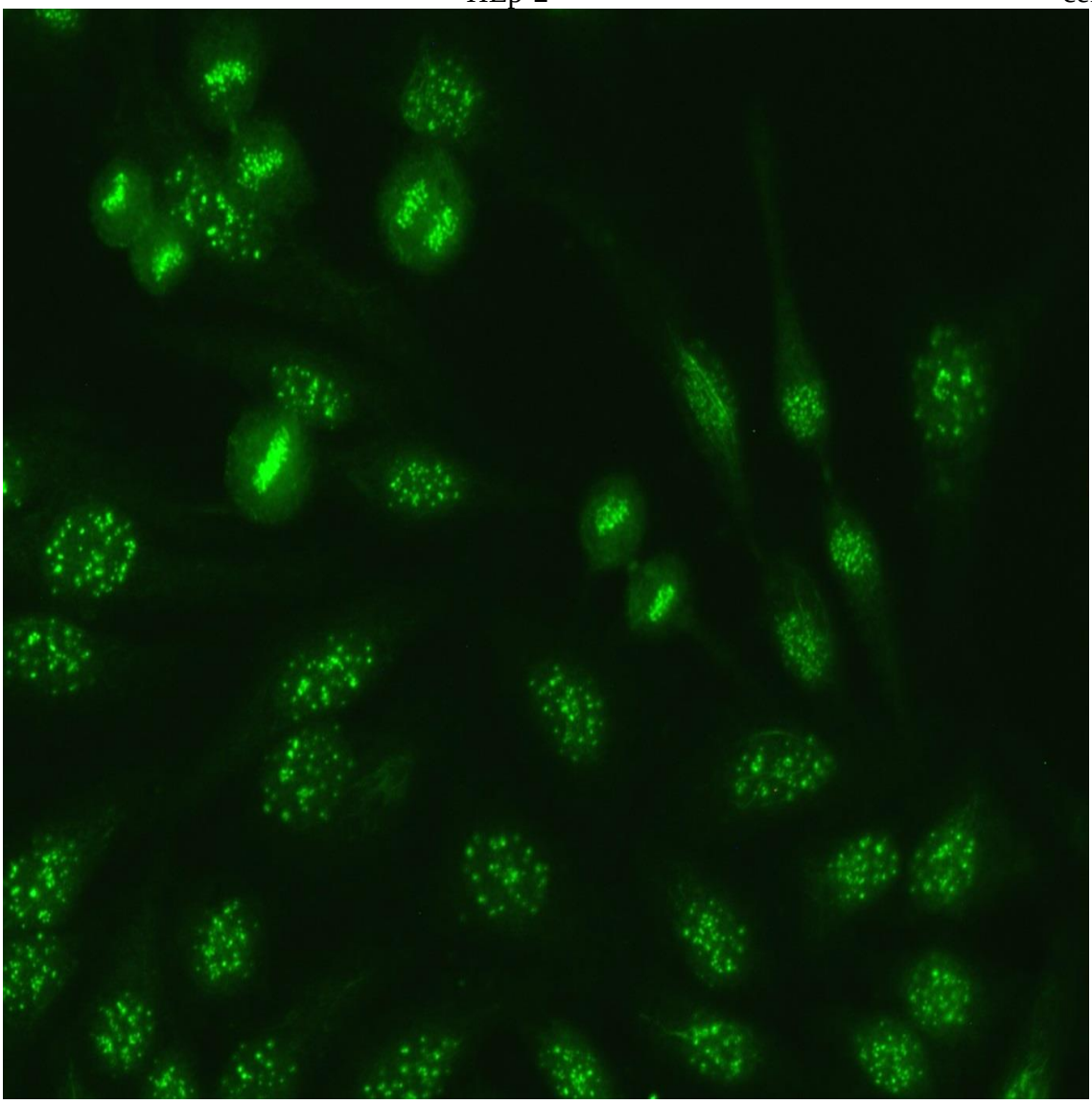

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Table 1. Clinical and epidemiological characteristics of the 236 included patients.

Characteristic (n = 236)	No. (%)
Gender	
Male	23 (9.7)
Female	213 (90.3)
Age (year, mean ± SD)	64.0 ± 14.4
Autoimmune diseases	
Systemic sclerosis	132 (55.9)
Primary biliary cirrhosis	22 (9.3)
Sjogren syndrome	17 (7.2)
Autoimmune hepatitis	11 (4.7)
Arthritis no RA	13 (5.5)
Rheumatoid arthritis (RA)	9 (3.8)
Systemic lupus erythematosus	7 (3.0)
Antiphospholipid syndrome	1 (0.4)
Thyroid disorders	9 (3.8)
Other	15 (6.4)
Overlap	18 (7.6)
Malignancy	
Breast	8 (25.7)
Haematological malignancy	4 (12.9)
Digestive malignancy	4 (12.9)
Cancer of unknown primary site	3 (9.7)
Gynecologic malignancy	3 (9.7)
Cutaneous malignancy	3 (9.7)
Renal neoplasm	2 (6.4)
Lung cancer	2 (6.4)
Pheochromocytoma	1 (3.3)
Oral cavity cancer	1 (3.3)

Table 2. Complementary tests realized.

Complementary test	No. (%)
Electrocardiogram	102 (43.2)
Chest radiography	207 (87.7)
Computed axial tomography (chest)	76 (32.2)
Spirometry	109 (46.2)
Upper endoscopic	65 (27.5)
Barium swallow	40 (16.9)
Echocardiogram	134 (56.8)
Right catheterism	7 (3.0)
Capillarioscopy	68 (28.2)