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Antinuclear antibodies in recurrent idiopathic pericarditis: Prevalence and clinical significance

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Abstract

Background: A positive result for antinuclear antibodies (ANA), often as a fortuitous observation, may be cause for concern in idiopathic recurrent pericarditis (IRP), nevertheless data are lacking on their prevalence and clinical significance. This study is sought to investigate the prevalence and clinical significance of ANA in IRP.
Methods: ANA titres were assessed in consecutive patients with recurrent pericarditis, and matched healthy controls. Baseline and follow-up data were recorded and compared according to ANA results.
Results: A total of 145 consecutive patients with recurrent pericarditis were studied: 122 patients with IRP, 23 patients with pericarditis due to known etiologies (rheumatologic diagnoses and postpericardiotomy syndrome), and 122 healthy controls. ANA were detected in 53 of 122 (43.4%) patients with IRP, and in only 12 of 122 (9.8%) controls ($p<0.001$). Low titres (1/40–1/80) were found in the majority of cases, while moderate positivity (1/160–1/320) was more common in patients with a known rheumatic disease (26.7% vs. 5.7%; $p=0.020$). High concentrations of ANA ($\geq$1/640) were not recorded. Women were at increased risk for ANA (OR 2.22 95%CI 1.07–4.60; $p=0.033$). During a mean follow-up of 32 months, complications and new diagnoses were similar in patients with or without ANA positivity.
Conclusions: Low-positive titres are more common in patients with IRP than in controls, suggesting a possible autoimmune pathogenesis. Nevertheless, they are often a clinically non-specific finding. Routine serologic testing for ANA suggests a source for recurrent pericarditis in less than 10% of cases, and in these cases other evidence typically suggests the underlying disease.

Keywords: Pericardium; Recurrent pericarditis; Antinuclear antibody

1. Introduction

In clinical practice antinuclear antibodies (ANA) are often performed in patients with acute and recurrent pericarditis as part of a routine aetiologic search [1–5].

A positive result for ANA, often as a fortuitous observation, may be cause for concern in recurrent pericarditis either for the

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physician or the patient, but final data on the prevalence and clinical importance of this finding are lacking.

The aim of this work is to study the prevalence and clinical significance of ANA in idiopathic recurrent pericarditis. To the best of our knowledge this is the first study specifically sought to evaluate this clinical question.

2. Materials and methods

2.1. Study population

This is a prospective observational study where all consecutive cases of recurrent idiopathic pericarditis were included between January 2001 and June 2005. Criteria for the diagnosis of recurrent pericarditis included: 1. documented first attack of acute pericarditis according to definite diagnostic criteria; 2. evidence of either recurrence or persistently active pericarditis. Recurrence was documented by recurrent pain and one or more of the following signs: pericardial friction rub, ECG changes, echocardiographic evidence of pericardial effusion, and elevations in erythrocyte sedimentation rate or C-reactive protein [6,7]. Different etiologies other than previous viral, idiopathic, and autoimmune pericarditis (including pericardial injury syndromes and connective tissue disease), were excluded. Patients with a known systemic autoimmune disease at baseline were separately considered as subgroup for comparison with patients with idiopathic recurrent pericarditis. The presence of a specific organ autoimmune disease, or other well recognized disorders associated with a positive ANA titre, such as chronic infectious diseases (i.e. mononucleosis, hepatitis C infection, subacute bacterial endocarditis, tuberculosis, and human immunodeficiency virus infection) and lymphoproliferative diseases was excluded in all cases.

An additional group of healthy age- and sex-matched controls was assessed in order to compare the frequency of ANA positivity in patients with idiopathic recurrent pericarditis vs. a sample of normal subjects. These controls had no evidence of inflammatory conditions.

2.2. Antinuclear antibodies

ANA were detected by indirect immunofluorescence on HEp-2 cells in two laboratories (Torino and Padova) according to current guidelines [8,9]. Anti-ENA (Extractable Nuclear Antigens) antibodies (anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB) were tested by counterimmunoelectrophoresis technique, using as control sera those provided by the Center for Disease Control (USA). ANA positivity was defined as a titre $\geq 1/40$. A low positive test was defined as titres of 1/40–1/80, a moderate positive test was considered with ANA titres of 1/160–1/320, and a high positive test was considered with a titre of ANA $\geq 1/640$. ANA titres were assessed at baseline and the result was confirmed at least once after 6–12 months.

ANA titres were assessed in patients with recurrent pericarditis, and healthy age- and sex-matched controls selected from healthy blood-donors of the same urban area. Baseline and follow-up data were recorded and compared according to ANA results. Rheumatoid factor was also tested in all patients according to current methods and guidelines.

2.3. Follow-up

During follow-up all new diagnoses in patients originally labelled as "idiopathic" were recorded. Follow-up visits were performed at 1 week, 1 month, 3 months, 6 months, 1 year and then yearly, if the course was uncomplicated. Follow-up data included at least focused history, physical examination and echocardiogram, while ECG and laboratory tests were considered if necessary according to clinical judgement.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation. Comparison between patients groups was performed using unpaired *t*-test for continuous variables and a chi-square analysis for categorical variables.

During follow-up we considered as adverse event the occurrence of recurrences, cardiac tamponade, and constrictive pericarditis. Nevertheless for time-to-event analysis, we only considered the recurrences, being the power of the study adequate to detect significant differences in the follow-up only for this event. A total of 92 patients, 46 in each group, was needed to detect a difference in the recurrence rate of 50.0% and 20.0% between the two groups (with or without a ANA positive test) with a power of 80% using a 2-sided $p=0.05$ level test. The estimated rates of recurrent pericarditis were based on the reported recurrence range (20 to 50%) with the hypothesis that a higher recurrence rate could be recorded in patients with a positive ANA test [2,5,6].

Time-to-event distributions were estimated by the Kaplan–Meier method and compared with the log-rank test. Logistic regression multivariate analysis was performed to evaluate independent predictors for a positive ANA titre in all patients with recurrent pericarditis. Variables included in the model were: age, gender, pericardial effusion, and etiology.

Statistical analysis was performed using SPSS 13.0 software (Chicago, Illinois). Odd ratios were given with 95% confidence intervals (CI). A p value of <0.05 was considered to show statistical significance.

3. Results

3.1. Characteristics of the study population

In the study period 145 patients (mean age 51.3 ± 16.6 years, 61 men) with recurrent pericarditis were studied and followed for a mean of 32 months (6 to 151 months): 122 patients with idiopathic recurrent pericarditis (mean age 51.0 ± 17.3 years, 54 men, female/male ratio 1.1), 8 patients with recurrent pericarditis following a postpericardiotomy syndrome (mean

Table 1
Comparison of baseline and follow-up data in patients with or without a known rheumatologic diagnosis.

Feature	Idiopathic etiology ($n=122$)	Rheumatologic disease* ($n=15$)	p
Baseline			
Mean age	51.0±17.3	54.1±10.6	0.499
Female gender	63 (51.6%)	12 (80.0%)	0.070
Pericardial effusion	98 (80.3%)	11 (73.3%)	0.768
ANA	53 (43.4%)	9 (60.0%)	0.345
ANA+ titre			
1/40–1/80 (low)	46 (37.7%)	5 (33.3%)	0.960
1/160–1/320 (moderate)	7 (5.7%)	4 (26.7%)	0.020
≥1/640 (high)	0 (0.0%)	0 (0.0%)	NS
Rheumatoid factor	5 (4.1%)	2 (13.3%)	0.365
Anti-Ro/SSA	5 (4.1%)	2 (13.3%)	0.365
Follow-up			
Further recurrences	33 (27.1%)	9 (56.3%)	0.043
Cardiac tamponade	1 (0.8%)	0 (0.0%)	0.545
Constriction	0 (0.0%)	0 (0.0%)	NS

ANA=antinuclear antibodies; *=recurrent pericarditis associated with a known connective tissue disease.

age 50.5±17.5 years, 4 men, female/male ratio 1.7), and 15 patients with a known rheumatologic diagnosis at baseline (mean age 54.1±10.6 years, 3 men, female/male ratio 4.0). An additional group of 122 healthy age- and sex-matched controls was tested for ANA and compared with patients with idiopathic recurrent pericarditis.

A comparison of baseline and follow-up data of patients with idiopathic recurrent pericarditis and pericarditis associated with a known connective tissue disease is reported in Table 1.

3.2. ANA titres

ANA were detected in 66 of 145 (45.5%) consecutive patients with recurrent pericarditis, and in 53 of 122 (43.4%) consecutive patients with idiopathic recurrent pericarditis.

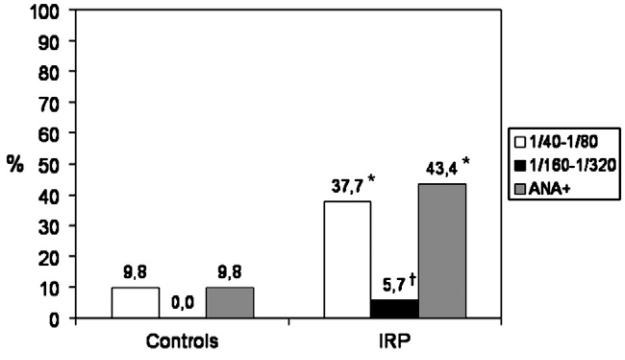

Fig. 1. Relative frequencies of ANA positivity in patients with idiopathic recurrent pericarditis (IRP) and healthy age- and sex-matched controls (controls vs. patients, respectively white bars: ANA 1/40–1/80, $p<0.001$*; black bars: ANA 1/160–1/320, $p=0.022^{\dagger}$; grey bars: overall ANA positivity, $p<0.001$*).

Table 2
Idiopathic recurrent pericarditis: comparison of baseline and follow-up data in patients with or without ANA positivity.

Feature	ANA+ ($n=53$)	ANA− ($n=69$)	p
Baseline			
Mean age	51.9±14.4	50.3±19.3	0.615
Female gender	34 (64.2%)	29 (42.0%)	0.024
Pericardial effusion	40 (75.5%)	50 (72.5%)	0.868
Corticosteroid use	19 (35.8%)	23 (33.3%)	0.924
Follow-up			
New diagnosis*	4 (7.6%)	4 (5.7%)	0.959
Further recurrences	16 (30.2%)	17 (24.6%)	0.628
Cardiac tamponade	0 (0.0%)	1 (1.5%)	0.920
Constriction	0 (0.0%)	0 (0.0%)	NS

ANA=antinuclear antibodies; *=new diagnoses were only rheumatologic.

ANA positivity was confirmed at least once after 6–12 months. No patients took any drug commonly associated with ANA positivity, and the baseline use of corticosteroids was similar in patients with idiopathic recurrent pericarditis with or without ANA positivity (35.8% vs. 33.3%, $p=0.924$).

Four of eight patients with recurrent pericarditis following postpericardiotomy syndrome had low ANA titre (respectively 50.0% vs. 43.4% in patients with idiopathic recurrent pericarditis, $p=0.997$).

A positive ANA titre was recorded in only 12 of 122 (9.8%) healthy controls ($p<0.001$ vs. patients with idiopathic recurrent pericarditis, see Fig. 1). In all cases normal subjects had a low titre (1/40 to 1/80).

Among patients with idiopathic recurrent pericarditis, a low-positive titre of ANA (1/40–1/80) was recorded in 46 patients (37.7%), while a moderate-positive titre (1/160–1/320) was observed in 7 patients (5.7%). High-positive titres (≥1/640) were not recorded. Rheumatoid factor and anti-ENA (in all cases anti-Ro/SSA) were more common in patients with a known rheumatologic disease (13.3% vs. 4.1%) at baseline. A comparison of baseline and follow-up data of patients with or without ANA positivity is reported in Table 2. In multivariable analysis (Table 3), women were at increased risk of ANA positivity (OR 2.22 95%CI 1.07 to 4.60; $p=0.033$). After a mean follow-up of 32 months, the complication rate (including further episodes of recurrent pericarditis, constrictive pericarditis, and cardiac tamponade) was similar irrespective of ANA positivity (Table 2 and Fig. 2).

Table 3
Multivariable analysis: independent predictors for a positive ANA titre in patients with recurrent pericarditis.

Variable	OR	95% CI	p
Age >50 years	0.82	0.41–1.65	0.581
Female gender	2.22	1.07–4.60	0.033
Pericardial effusion	1.90	0.95–3.82	0.791
Non-idiopathic etiology	1.13	0.46–2.79	0.069

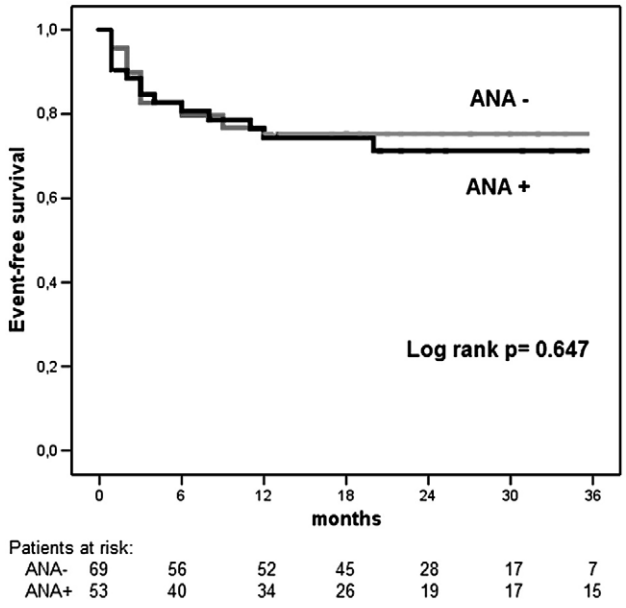

Fig. 2. Idiopathic recurrent pericarditis: event-free survival in patients with or without ANA positivity (95% confidence intervals for the survival curve point estimations at 24 months were respectively 0.66 to 0.86 for ANA−, and 0.58 to 0.86 for ANA+; $p=0.259$). Recurrent pericarditis was the adverse event.

3.3. New diagnoses

At baseline, a known connective tissue diseases was present in 15 cases: respectively, Systemic Lupus Erythematosus (SLE) in 7 patients, Rheumatoid Arthritis (RA) in 3 patients, Polymyalgia Reumatica in 2 patients, Sjögren's Syndrome (SS), Sclerodermia, and Behcet's disease were recorded in one case for each disease. New diagnoses were reached in 8 of 122 cases initially labelled as "idiopathic" (6.6%), and were only rheumatological: five cases of SS (all positive for anti-Ro/SSA), and one case for each of the following: Rheumatoid Arthritis, Polymyalgia Reumatica, and Giant Cell Temporal Arteritis. They were equally distributed between ANA positive and ANA negative patients (see Table 2).

4. Discussion

ANA are present in a wide array of systemic autoimmune diseases, organ-specific autoimmune diseases, and infections. When used correctly, they may provide valuable diagnostic and prognostic information; however their presence does not mandate the presence of illness, since they can also be found in otherwise normal individuals [10]. Actually they represent a diagnostic criterion only for SLE [8,11]. ANA show a low specificity (ranging from 41% to 63%), and a variable sensitivity (high up to 93% for SLE, but as low as 41% for RA) [8]. While ANA have a high sensitivity in SLE, in which a negative ANA make the probability of the disease unlikely, the low sensitivity and specificity of the ANA in other connective tissue diseases make the ANA a weak test for ruling in or ruling out other rheumatologic diseases such as RA, SS, Polymyositis, and Dermatomyositis. ANA may be found in several connective tissue diseases, chronic infections, in 5 to 10% of normal subjects, and can be associated with several medications [11]. ANA titres are important in the interpretation of the test but fluctuations in their titres have little clinical relevance in autoimmune diseases [8,11]. In one study of 125 subjects with a positive ANA but no other evidence of connective tissue disease, titres greater than 1:40 were seen in 32%, greater than 1:80 were seen in 13%, and greater than 1:320 were only seen in 3% of patients [10]. While the presence of high titres of antibodies ($\geq 1/640$) should arouse suspicion of an autoimmune disorder, low titres of antibody ($\leq 1:80$) with no signs or symptoms of disease are generally a non-specific finding, more common in women and elderly, as well as in patients with organ-specific autoimmune diseases [11].

This study confirms that ANA positivity is not uncommon in patients with idiopathic recurrent pericarditis, suggesting the possible role of an autoimmune pathogenesis of the disease, often presumed, at least in a subgroup of patients [5,12,13]. ANA positivity was generally found with a low-positive result (1/40–1/80) in about 40% of cases of recurrent idiopathic pericarditis. Female gender is associated with an increased risk of ANA positivity (OR 2.22). Higher titres were associated with known connective tissue diseases.

Despite a frequent ANA positivity, new diagnoses, always rheumatologic, were found during the follow-up in only 6.6% of cases, and were equally distributed between ANA positive and ANA negative patients. On this basis, low-positive ANA results are a non-specific finding in the majority of patients with idiopathic recurrent pericarditis. Routine serologic testing for ANA and rheumatoid factor is of little clinical utility in these patients and suggests a source for recurrent pericarditis in less than 10% of cases, and in these cases other evidence typically suggests the underlying disease [1]. SLE is often mentioned as a cause of recurrent pericarditis [1,12,13]. Our study shows that in idiopathic recurrent pericarditis, the most common new diagnosis was not SLE, as commonly believed, but primary SS, an olygosymptomatic disease, often overlooked, characterized by sicca syndrome and positivity for anti-SSA antibodies, and that should be considered in these patients based on our results.

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