Clinical significance of HEp-2 cell cytoplasmic patterns in anti-neutrophil cytoplasmic antibody associated vasculitis

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Abstract
The study was to investigate the clinical characteristics and significance of antinuclear antibody (ANA) cytoplasmic patterns in ANCA-associated vasculitis (AAV) from Southwest China.

A retrospective study including 232 AAV patients from Peoples Hospital of Deyang City was performed. These included 115 patients with ANA cytoplasmic pattern as observation group and 117 patients without ANA cytoplasmic pattern as control group.

Chest involvement (60.00 vs 46.15, P = .035), cardiovascular involvement (5.21 vs 29.91, P < .001), and renal involvement (37.39 vs 77.78, P = .001) were different between groups.

Total protein (69.55 vs 64.01, P < .001), triglyceride (1.41 vs 1.18, P = .023), mean cell volume (89.76 vs 87.59, P = .040), and estimated glomerular filtration rate (76.67 vs 50.87, P = .035) were higher in ANA cytoplasmic patterns group. Creatinine (73.00 vs 117.50, P = .011), white blood cell (6.93 vs 8.86, P = .001), platelet (196.0 vs 239.0, P = .017), anti-myeloperoxidase (2.44 vs 3.42, P = .042), and anti-proteinase 3 (1.00 vs 4.93, P = .007) were lower in this group. In multivariate analysis, creatinine (odds ratio [OR] = 1.21, 95% confidence interval [CI]: 1.06–1.38), triglyceride (OR = 1.97, 95% CI: 1.10–3.48), and anti-myeloperoxidase (OR = 1.64, 95% CI: 1.37–1.95) were independent risk factors of AAV renal involvement. Total protein (OR = .95, 95% CI: 0.91–0.99) was an independent protective factor of AAV renal involvement. Chi-square test showed that speckled pattern was different among anti-neutrophil cytoplasmic antibody patterns (χ² = 18.526, P < .001).

In summary, HEp-2 cell cytoplasmic patterns have certain clinical significance in AAV, which is a new exploration of the clinical value of ANA.

Abbreviations: aANCA = atypical ANCA, AAV = ANCA-associated vasculitis, ANA = antinuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, BVAS = Birmingham Vasculitis Activity score, cANCA = cytoplasmic ANCA, CI = confidence interval, eGFR = estimated glomerular filtration rate, IIF = immunofluorescent, MPA = microscopic polyangiitis, MPO = anti-myeloperoxidase, OR = odds ratio, pANCA = perinuclear ANCA, PR3 = anti-proteinase 3, RR = rods and rings.

Keywords: anti-neutrophil cytoplasmic antibody, antinuclear antibody, fluorescence pattern, HEp-2 cell cytoplasmic pattern, vasculitis

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic auto-inflammatory disorder and indirect immunofluorescence (IIF) is the most common assay for ANCA.[1] ANCA fluorescence patterns included cytoplasmic ANCA (cANCA), perinuclear ANCA (pANCA), and atypical ANCA (aANCA).[2,3] Previous studies have pointed out a high positive rate of antinuclear antibody (ANA) in patients with AAV.[4–6] In addition, the fluorescence pattern of IIF-ANA is usually ignored as an interference factor for the detection of ANCA and will not be studied further. As the most widely used...
biomarker of autoimmune diseases, HEp-2 cell cytoplasmic pattern of ANA is of great significance. In August 2014, the International Consensus on antinuclear antibody pattern meeting made clear that cytoplasmic patterns were categorized as a major group and required patterns including fibrillar (AC-15, 16, 17), speckled (AC-18, 19, 20), reticular/AMA (AC-21), polargolgi-like (AC-22), and rods and rings (RR) (AC-23). Studies on HEp-2 cell cytoplasmic patterns mainly focus on autoimmune diseases, and the clear patterns are RR, polargolgi-like and reticular/AMA at present. The clinical significance of other required fluorescence patterns are not clear yet. The multivariate analysis showed significant associations (7.4%–29.6%) between anti-RR pattern and “time of exposure to interferon and ribavirin”. The combination of anti-cytoplasmic autoantibody and Jo-1 showed high sensitivity (92%) and specificity (89%) for the identification of antisyndrome patients. In the elderly group (60–76 years old), the positive rate of cytoplasmic patterns accounted for 17.2% of the total Thai healthy participants, second only to the spot pattern (20.6%), suggesting that ANA cytoplasmic patterns were related to the age of patients. However, there have been rare studies on ANA cytoplasmic patterns in AAV. Here we performed a retrospective study, aiming to investigate the clinical characteristics and significance of HEp-2 cell cytoplasmic patterns, as well as the correlation between ANA cytoplasmic patterns and ANCA patterns in patients with AAV from Southwest China.

2. Materials and methods

2.1. Study design and population

We performed a retrospective study on the AAV patients from Peoples Hospital of Deyang City from January 2009 to December 2019. AAV was diagnosed by 2 experienced rheumatologists based on the definitions of the Chapel Hill nomenclature. Patients who were diagnosed as vasculitis associated with connective tissue disease, vasculitis secondary to drugs of allergic disease and viral infections (hepatitis B, cytomegalovirus and herpes simplex virus), without complete data were excluded. Finally, 232 patients were included, including 115 patients with ANA cytoplasmic pattern as observation group and 117 patients without ANA cytoplasmic pattern as control group. Written informed consent was signed by all patients. This study was approved by the Ethics Committee of Peoples Hospital of Deyang City (Registration number: ChiCTR2000032468) and was based on the principles of the 1964 Declaration of Helsinki and its later amendments. An informed consent for using their clinical characteristics and laboratory data was obtained from all cases enrolled.

2.2. Definition of cytoplasmic pattern

HEp-2 cell ANA cytoplasmic patterns were assessed by 2 experienced medical laboratory technicians based on the patterns at the International Consensus on antinuclear antibody pattern website (www.ANApatterns.org). ANA and ANCA were tested using the IIF assay. The fluorescence patterns were photographed using an optical light microscope (Olympus Microscope System BX51, Japan). Mixed pattern was defined as the presence of two or more fluorescence patterns in the same serum sample. Titer was defined as the highest dilution at which specific fluorescence was observed. According to the indication of the manufacturer, a negative titer was defined as no fluorescence. “Observation group” was defined as follows: (1) all patients were clinically diagnosed with AAV; (2) ANCA pattern was positive and ANA pattern was positive in cytoplasm; (3) if ANA pattern was mixed, cytoplasmic pattern was the main pattern. “Control group” was defined as follows: (1) all patients were clinically diagnosed with AAV; (2) ANCA pattern was positive and ANA pattern was negative in cytoplasm; (3) if ANA pattern was mixed, cytoplasmic fluorescence pattern did not include.

2.3. Clinical data

Demographic and clinical data were collected from the medical records. Clinical characteristics included age, gender, time from the onset of symptoms to definitive diagnosis, disease activity, laboratory data and symptoms. Disease activity of AAV was evaluated by Birmingham Vasculitis Activity score (BVAS). Laboratory data included routine blood tests, related biochemical indexes, coagulation function and immune-related biomarker. Serum samples were tested for ANCA and ANA by IIF assay. Anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) were tested by chemiluminescence immunoassay. Routine blood tests, related biochemical indexes and coagulation function were performed according to the manufacturers’ instructions.

2.4. Statistical analysis

The statistical analyses were applied by using the statistical package for the social sciences software (version 22.0). Quantitative data were tested by Shapiro-Wilk normal test. Normally distributed data were presented as mean ± standard deviation, non-normal variables were expressed as median (interquartile range). Categorical variables were presented as percentage and frequency. Comparison between groups was evaluated with two independent sample T test for continuous variables with non-normal distribution, while Mann-Whitney U test was used for continuous variables with non-normal distribution. Correlation analysis between ANA titer and renal damage was evaluated with spearman rank test. Odds ratio (OR) and 95% confidence interval (CI) of clinically significant variables with a P < .05 in between-group comparison were adjusted by multivariate logistic regression. The correlation between ANCA patterns and cytoplasmic patterns were analyzed by row × column chi-square test. Bonferroni method was used for pair comparison. A P < .017 was considered statistically significant.

3. Results

3.1. Demographics of the population

The demographics and clinical characteristics of all the individuals were illustrated in Table 1. A total of 232 AAV patients were included, including 184 (79.31%) microscopic polyangiitis (MPA), 37 (15.95%) granulomatosis with polyangiitis and 11 (4.74%) eosinophilic granulomatosis with polyangiitis. The ratio of male (19.13% vs 62.39%, P < .001) in the observation group was lower than the control group. Chest involvement (including cough, expectoration, hemoptysis,
3.4. Factors associated with renal damage in AAV patients

Results of multivariate analysis in AAV patient with or without renal damage were presented in Table 4. All the AAV patients were classified into the non-decreased eGFR and decreased eGFR groups using a cut-off value of ≥90 ml/min/1.73 m². Variables with P < .05 were included in multivariate logistic regression analysis. Several clinical and laboratory variables were associated with renal damage in AAV patients. Creatinine (OR = 1.21, 95% CI: 1.06–1.38, P = .01), triglyceride (OR = 1.97, 95% CI: 1.10–3.48, P = .02), white blood cell (OR = 1.09, 95% CI: 1.01–1.19, P = .04), and anti-MPO (OR = 1.21, 95% CI: 1.06–1.38, P < .001) were independent risk factors of AAV renal involvement. While total protein (OR = .95, 95% CI: 0.91–0.99, P = .03) was an independent protective factor of AAV renal involvement.

3.5. Correlation between IIF-ANA cytoplasmic patterns and IIF-ANCA patterns

All the 232 patients including 167 (71.98%) pANCA, 35 (15.09%) cANCA and 30 (12.93%) aANCA were illustrated in Table 5. Correlations between IIF-ANA cytoplasmic patterns and IIF-ANCA patterns were illustrated by row × column chi-square test. The percentage of speckled (AC-18, 19, 20) was the highest among the three IIF-ANCA patterns. The percentage of speckled (AC-18, 19, 20) was 47.90% (80/167) in pANCA pattern, 8.57% (3/35) in cANCA pattern and 40.00% (12/30) in aANCA pattern respectively. Chi-square test indicated that the rate of speckled in different ANCA patterns was statistically significant (χ² = 18.526, P < .001). Reticular/AMA (AC-21) was not detected in any of the three ANCA patterns. There were no statistically differences in terms of RR (AC-18), fibrillar (AC-15, 16, 17), and polar/Golgi-like (AC-22).

4. Discussion

A variety of autoantibodies can be detected in AAV patients. IIF was the first method used and is still the most commonly used ANCA and ANA at present. Previous studies showed that IIF-ANCA was easy to cover up with high titer ANA.
**Table 2**
Comparison of laboratory data in the different groups.

| Laboratory data | Observation group, median (IQR/SD) | Control group, median (IQR/SD) | V/Z | P  |
|-----------------|------------------------------------|-------------------------------|-----|----|
| Total bilirubin (μmol/L) | 7.50 (5.00, 11.50) | 7.65 (6.10, 10.77) | −0.195 | .845 |
| Direct bilirubin (μmol/L) | 2.60 (1.90, 4.42) | 3.10 (2.10, 4.75) | −0.830 | .407 |
| Total protein (g/L) | 69.55 ± 10.41 | 64.01 ± 8.67 | 4.213 | <.001 |
| Albumin (g/L) | 33.56 ± 6.34 | 33.71 ± 6.57 | −0.165 | .869 |
| Alanine aminotransferase (U/L) | 17.00 (9.00, 32.25) | 16.00 (9.25, 29.00) | −0.589 | .556 |
| Aspartate aminotransferase (U/L) | 24.00 (16.75, 39.00) | 22.00 (16.00, 32.00) | −1.493 | .136 |
| r-glutamyl transferase (U/L) | 28.50 (14.75, 57.75) | 30.50 (14.00, 51.50) | −0.381 | .703 |
| Lactic dehydrogenase (U/L) | 219.00 (172.50, 281.50) | 218.00 (161.00, 285.00) | −0.508 | .612 |
| Total bile acid (μmol/L) | 3.00 (1.60, 6.15) | 3.25 (1.70, 6.25) | −0.381 | .703 |
| Creatinine (μmol/L) | 73.00 (51.75, 279.50) | 117.50 (66.25, 413.25) | −2.543 | .011 |
| Urea (mmol/L) | 7.00 (4.08, 15.23) | 9.03 (4.92, 20.67) | −1.652 | .098 |
| Cholesterol (mmol/L) | 341.00 (241.25, 467.50) | 316.96 (224.25, 442.25) | −1.322 | .186 |
| Cystatin C (mg/L) | 1.45 (1.07, 3.11) | 1.69 (1.01, 3.93) | −0.316 | .752 |
| eGFR (mL/min/1.73m²) | 76.67 (12.65, 107.58) | 50.87 (10.83, 101.54) | 2.121 | .035 |
| Total protein (g/L) | 1.41 (0.94, 1.91) | 1.18 (0.82, 1.64) | −2.276 | .023 |
| Total cholesterol (mmol/L) | 3.89 (3.15, 4.51) | 3.91 (3.01, 4.68) | −0.159 | .874 |
| HDL (mmol/L) | 1.02 (0.73, 1.24) | 1.10 (0.72, 1.40) | −0.966 | .334 |
| LDL (mmol/L) | 2.11 (1.50, 2.58) | 2.14 (1.52, 2.64) | −0.530 | .596 |
| Total bile acid (μmol/L) | 6.93 (4.62, 9.53) | 8.86 (6.94, 12.33) | −3.414 | .001 |
| Red blood cell (x10¹²/L) | 3.48 ± 0.94 | 3.48 ± 0.94 | −0.441 | .659 |
| RBC-SD (fl) | 48.85 (44.45, 54.55) | 47.30 (44.35, 51.75) | −1.884 | .060 |
| RBC-CV (%) | 15.79 (14.00, 16.60) | 15.34 (13.80, 16.47) | −1.195 | .236 |
| HGB (g/L) | 97.93 ± 22.21 | 98.59 ± 26.18 | 0.052 | .959 |
| HCT (%) | 0.31 ± 0.07 | 0.30 ± 0.09 | 0.176 | .861 |
| MCHC (g/L) | 89.76 ± 7.62 | 87.59 ± 7.59 | 2.071 | .040 |
| MCH (pg) | 28.75 (27.50, 30.40) | 28.37 (26.90, 30.00) | −1.115 | .265 |
| MCV (fl) | 320.39 ± 16.17 | 320.83 ± 14.90 | −0.255 | .799 |
| Platelet (x10¹²/L) | 196.0 (120.0, 270.5) | 239.0 (158.0, 317.0) | −2.388 | .017 |
| Anti-MPO (RU/ml) | 2.44 ± 1.98 | 3.42 ± 2.11 | −2.009 | .042 |
| Anti-PR3 (RU/ml) | 1.00 (1.00, 1.65) | 1.93 (1.00, 1.10) | −2.703 | .007 |

Anti-MPO = anti-myeloperoxidase antibodies, Anti-PR3 = anti-proteinase 3 antibodies, APTT = activated partial thromboplastin time, eGFR = estimated glomerular filtration rate, HDL = high density lipoprotein, IQR = interquartile range, LDL = low density lipoprotein, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, ROW = red blood cell distribution width, SD = standard deviation.

* P < .05.

ANCA display lower specificities. Therefore, ANA was generally considered to be an interference factor for IIF-ANCA, and the clinical significance of ANA in AAV patients was usually ignored. Compared with anti-nuclear autoantibodies, there were few reports on anti-cytoplasmic patterns, especially in AAV.[18] This study focused on the significance of HEp-2 cell cytoplasmic pattern in AAV clinical features and laboratory test results. Some characteristics of HEp-2 cell cytoplasmic pattern in the Southwest Chinese AAV patients were notable.

**Table 3**
Spearman correlation analysis between ANA titer and renal involvement in AAV patients.

| Laboratory data | P  | r  |
|-----------------|----|----|
| Creatinine (μmol/L) | .046* | −0.191 |
| eGFR (mL/min/1.73m²) | .050 | 0.188 |
| Urea (mmol/L) | .086 | −0.165 |
| Cholesterol (mmol/L) | .386 | 0.020 |
| Cystatin C (mg/L) | .535 | −0.060 |

AAP = ANCA-associated vasculitis, ANA = antinuclear antibody, eGFR = glomerular filtration rate.

* P < .05.

MPA was the most frequent in AAV.[19,20] In the current study, 79.3% of AAV was diagnosed with MPA. Previous studies have indicated that the positivity rate of ANA was higher in females than that in males.[21,22] In addition, some case reports also supported that ANA usually occurred in females AAV patients.[23,24] These results suggest a possible link between gender and ANA in AAV.[25] Therefore, this study excluded secondary vasculitis, such as connective tissue disease, drug-induced vasculitis and other factors.

In this study, BVAS was used to evaluate AAV activity. However, there was no statistically significant difference between the positive and negative groups. Concerning clinical symptoms, the incidence of chest involvement (pulmonary nodules/fibrosis, pleurisy, hemoptysis), cardiovascular involvement (pericarditis, recent myocardial infarction, chronic heart failure) and renal involvement were significantly associated with anti-cytoplasmic autoantibodies. We speculated that ANA+ AAV patients may have clinical manifestations of co-existence of cardiovascular damage and kidney damage. Metabolites of tryptophan may also cause atherosclerosis through the release of reactive oxygen species that cause endothelial damage.[26] Uremic pericarditis, pericardial effusion and chronic...
left heart failure were common clinical manifestations in patients with end stage renal disease.\cite{27} It was suggested that accumulation of toxic metabolites may play an important role in cardiovascular damage in end stage renal disease patients.\cite{28}

These studies showed that there were close relationships between cardiovascular involvement and renal involvement in AAV patients.\cite{29,30} Conventional laboratory results showed that indicators of renal damage (e.g., creatinine, eGFR, etc.) were significantly different between the anti-cytoplasmic autoantibody positive group and negative group. Spearman rank test suggested that there was a correlation between antibody titers and renal damage. However, this correlation was weak. Further logistic regression analysis showed that total protein, creatinine, triglyceride, white blood cell and anti-MPO were independent risk factors for renal damage. There may be problems with collinearity among them. The variance inflation factor values are all less than 5, indicating no excessive multicollinearity among the covariates. Therefore, we believe that although ANA titer is related to renal damage, ANA titer is not an independent risk factor for it.

In anti-cytoplasmic karyotype analysis, reticular/AMA (AC-21) was not detected in any of the three ANCA patterns. The other four types of fluorescent karyotypes had different degrees of positive rates. Speckled (AC-18, 19, 20) of IIF-ANA cytoplasmic patterns tended to appear in pANCA and aANCA, while the positive rate was lower in cANCA. Whether cytoplasmic granule type can be an auxiliary indicator for ANCA karyotype determination has not been reported in the literature. Because IIF-ANA can be asymptomatic for many years before presenting with clinical symptoms, it is worth examining whether IIF-ANA cytoplasmic patterns also have a suggestive effect on clinically asymptomatic patients with early AAV.

Our study had certain limitations. The prevalence of infection may be underestimated due to the selection bias since outpatients with infection were automatically excluded. Additionally, data were generated from one hospital from Southwest China. The interpretation of the results to the general AAV population is cautious. In addition, we have not conducted in-depth studies on the mechanism of ANA cytoplasmic pattern in AAV patients. Whether ANA plays a role in the pathogenesis of AAV needs to be further verified by in vitro models. Further studies with large sample size, multi-center and long-term follow-up are needed to verify our observations.

5. Conclusions

In summary, HEp-2 cell cytoplasmic patterns have certain clinical significance and certain reference values in AAV, which is a new exploration of the clinical value of autoantibodies and worthy of drawing the attention of clinicians.

**Author contributions**

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