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Evaluation of ANCA in vasculitis and non-vasculitis diseases

ANCA'nın vaskülit ve vaskülit dışı hastalıklarda değerlendirilmesi

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Abstract

Purpose: The present study aims to evaluate the existence of anti-neutrophil cytoplasmic antibody (ANCA) in vasculitis and non-vasculitis diseases.

Materials and methods: Over five years, the results of 5107 serum samples submitted to the Medical Microbiology Laboratory for ANCA evaluation were retrospectively analyzed. The existence of ANCA was studied using the preparations containing ethanol-fixed and formalin-fixed granulocyte substratum by indirect immunofluorescence (IIF) testing method; and myeloperoxidase (MPO) and Proteinase-3 (PR-3) antigens in ANCA-positive samples were studied with the ELISA method.

Results: 422 (8.3%) of the samples were considered ANCA-positive. The mean age of ANCA-positive patients was found significantly high from ANCA-negative patients (p=0.0001). ANCA-positivity was 6.7% in men and 9.4% in women. A statistically significant difference was detected between women and men in terms of ANCA positivity (p=0.0001). 62 (19.9%) of the 312 patients diagnosed with vasculitis and 360 (7.5%) of the 4795 patients with non-vasculitis were ANCA-positive. The age of ANCA-associated vasculitis (AAV) patients was statistically high compared to non-AAV patients (p=0.0001). ANCA-positivity was found 16.7% in patients with IgA vasculitis, 18.6% in leukocytoclastic vasculitis, 56.9% in rheumatoid arthritis, 46.9% in systemic lupus erythematosus, 18.6% in interstitial pulmonary disease, 7.7% multiple sclerosis, 10.2% in chronic renal failure, and 5.1% in cerebrovascular accident.

Conclusion: In vasculitis cases, ANCA positivity rate was higher than in non-vasculitis diseases. In non-vasculitis diseases, the target antigen MPO-ANCA and PR3-ANCA positivity was rare compared to vasculitis cases. Among ANCA-positive patients, the most common non-vasculitis diseases included connective tissue disease, chronic renal failure and interstitial pulmonary disease.

Keywords: Anti-neutrophil cytoplasmic antibody, MPO-ANCA, PR3-ANCA, vasculitis, connective tissue disease.

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Öz

Amaç: Bu çalışma, vaskülit ve vaskülit dışı hastalıklarda anti-nötrofil sitoplazmik antikorun (ANCA) varlığını değerlendirmeyi amaçlamaktadır.

Gereç ve yöntem: Beş yılı aşkın bir sürede ANCA değerlendirmesi için Tıbbi Mikrobiyoloji Laboratuvarına gönderilen 5107 serum örneğinin sonuçları retrospektif olarak incelendi. ANCA'nın varlığı, etanolle fikse edilmiş ve formalinle fikse edilmiş granülosit substrat içeren preparatlar kullanılarak indirekt immünofloresan (IIF) test yöntemiyle araştırıldı; ANCA pozitif örneklerde miyeloperoksidaz (MPO) ve Proteinaz-3 (PR-3) antijenleri ELISA yöntemi ile çalışıldı.

Bulgular: Örneklerin 422'si (%8,3) ANCA-pozitif olarak değerlendirildi. ANCA pozitifliği erkeklerde %6,7 ve kadınlarda %9,4 idi. ANCA pozitifliği açısından kadın ve erkekler arasında istatistiksel olarak anlamlı fark saptandı (p=0,0001). ANCA pozitif hastaların ortalama yaşı ANCA negatif hastalardan anlamlı olarak yüksek bulundu (p=0,0001). Vaskülit tanısı alan 312 hastanın 62'si (%19,9) ve vasküliti olmayan 4795 hastanın 360'ı (%7,5) ANCA pozitifti. AAV hastalarının yaşı, AAV olmayan hastalara göre istatistiksel olarak yüksekti (p=0,0001).

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ANCA pozitifliği IgA vaskülitlerinde %16,7, lökositoklastik vaskülitlerde %18,6, romatoid artritte %56,9, sistemik lupus eritematozusta %46,9, interstisyel akciğer hastalığında %18,6, multipl sklerozda %7,7, kronik böbrek yetmezliğinde %10,2 ve serebrovasküler olayda %5,1olarak bulunmuştur.
Sonuç: Vaskülit olgularında ANCA pozitiflik oranı, vaskülit dışı hastalıklara göre daha yüksekti. Vaskülit dışı hastalıklarda hedef antijen MPO-ANCA ve PR3-ANCA pozitifliği vaskülit vakalarına göre nadirdi. ANCA-pozitif hastalar arasında en yaygın vaskülit dışı hastalıklar bağ dokusu hastalığı, kronik böbrek yetmezliği ve interstisyel akciğer hastalığıydı.

Anahtar kelimeler: Anti-nötrofil sitoplazmik antikor, MPO-ANCA, PR3-ANCA, vaskülit, bağ dokusu hastalığı.

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Introduction

Antineutrophil cytoplasmic antibodies (ANCA) are a group of autoantibodies that are predominantly formed against proteins expressed in cytoplasmic granules of neutrophils. It is recognized as a laboratory test that is commonly used in the diagnosis of patients with suspected vasculitis [1]. ANCA-associated vasculitis (AAV) is characterized by inflammation of small- to medium-sized blood vessels. It includes a variety of clinicopathologies, including polyangiitis granulomatosis (GPA), microscopic polyangiitis (MPA), polyangiitis eosinophilic granulomatosis (EGPA) and vasculitis associated with renal-limited ANCA [2].

Anti-neutrophil cytoplasmic antibodies are not a specific indicator for AAV, because these autoantibodies can also be detected in different diseases [1]. They are thought to have clinical, pathogenic and/or diagnostic significance in certain diseases as well as ANCA-associated vasculitis [3].

The presence of ANCA can be screened with indirect immunofluorescence (IIF) [4]. It is reported as two main patterns, namely the cytoplasmic pattern (C-ANCA) and the perinuclear pattern (P-ANCA) [3]. Proteinase-3 (PR-3) is the main target antigen of C-ANCA, while myeloperoxidase (MPO) is the P-ANCA's primary target antigen. In addition, P-ANCA's target antigens may include elastase, cathepsin G, lactoferrin and lysozyme [4]. It is recommended to look for antigen-specific ANCA targeting PR-3 and MPO in any patients suggesting ANCA-associated vasculitis, and for ANCA in patients with anti-glomerular basal membrane disease, idiopathic interstitial pneumonia and nephritis-associated infective endocarditis [3]. The present study aimed to evaluate ANCA positivity in vasculitis and non-vasculitis diseases.

Materials and methods

The results of 5107 serum samples sent to Medical Microbiology laboratory between 01/01/2015 and 31/12/2019 for ANCA evaluation were retrospectively analyzed. Repeated samples of the same patient were excluded. The existence of ANCA was investigated using preparations that contained ethanol-fixed and formalin-fixed granulocyte substrate (Euroimmun, Lübeck, Germany) by the indirect immunofluorescence (IIF) testing method in accordance with the manufacturer's recommendations (in 1/10 serum dilations). The results were evaluated as C-ANCA and P-ANCA. The MPO antigens (AESKULISA® MPO, Aesku Diagnostics, Wendelsheim, Germany) and the PR3 antigens (AESKULISA® PR3 sensitive, Aesku Diagnostics, Wendelsheim, Germany) of the positive samples were studied with ELISA method.

The demographic data of the patients were obtained from the hospital's information system. Study was conducted with the approval of the ethics board for Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Statistical analyses

The statistical analysis of data was performed with SPSS 25.0 package program. Categoric variables were expressed in numbers and percentages and continuous variables were expressed in mean ± standard deviation, minimum and maximum values. The differences between the categorical variables were examined with the Chi-square analysis and the Mann-Whitney U-test was used to perform cross-group comparisons.

Results

In total, 5107 serum samples were evaluated within the scope of the study. 2904 (56.9%) of the samples were taken from female patients. The mean age was 47.7±20.28 years (min: 3, max: 94). 422 (8.3%) of the samples were considered ANCA-positive. The mean age for positive samples was 53.54±21.39 (min:3, max:92), and 47.17±20.1 for negative samples (min:3, max:94). The mean age of ANCA-positive patients was found significantly different from ANCA-negative patients (p=0.0001)

ANCA-positivity was 6.7% in men and 9.4% in women. A statistically significant difference was detected between women and men in terms of ANCA positivity (p=0.0001). P-ANCA positivity was found in 314 (6.2%) patients, and C-ANCA positivity in 108 (2.1%).

In 62 (19.9%) of the 312 patients diagnosed with vasculitis and 360 (7.5%) of the 4795 patients with non-vasculitis diseases, ANCA-positivity was detected (Table 1, 2).

ANCA-associated vasculitis was classified as follows: GPA, MPA, renal-localized ANCA and ANCA-associated vasculitis [2] (Table 1). An evaluation of 422 ANCA-positive patients showed that 27 (6.4%) patients with ANCA-positive vasculitis had ANCA-associated vasculitis, 15 (3.6%) had IgA vasculitis (HSP) and 8 (1.9%) had leukocytoclastic vasculitis.

Table 1. ANCA evaluation in vasculitides

Vasculitis	ANCA n (%)		Positive ANCA n (%)		MPO positive n (number of tests)	PR3 positive n (number of tests)
	Negative	Positive	P ANCA	C ANCA		
Vasculitis (undiagnosed) N=49	45 (91.8)	4 (8.2)	2 (50)	2 (50)	0 (4)	1 (4)
ANCA-associated vasculitis (undiagnosed) N=6	1 (16.7)	5 (83.3)	4 (80)	1 (20)	5 (5)	0 (5)
GPA* N=17	0 (0)	17 (100)	6 (35.3)	11 (64.7)	5 (16)	11 (16)
MPA N=4**	2 (50)	2 (50)	2 (100)	0 (0)	2 (2)	0 (2)
Renal-limited ANCA associated vasculitis N=6	3 (50)	3 (50)	2 (66.7)	1 (33.3)	2 (3)	1 (3)
Leukocytoclastic vasculitis N=43	35 (81.4)	8 (18.6)	5 (62.5)	3 (37.5)	0 (6)	0 (6)
IgA vasculitis N=90	75 (83.3)	15 (16.7)	10 (66.7)	5 (33.3)	0 (10)	0 (9)
Urticarial vasculitis N=6	5 (83.3)	1 (16.7)	1 (100)	0 (0)	0 (1)	0 (0)
Takayasu N=20	18 (90)	2 (10)	2 (100)	0 (0)	1 (2)	0 (2)
Behcet's disease N=71	66 (93)	5 (7)	3 (60)	2 (40)	1 (5)	0 (2)
Total N=312	250 (80.1)	62 (19.9)	37 (59.7)	25 40.3)	16 (54)	13 (48)

*GPA: Granulomatosis with Polyangiitis, **MPA: Microscopic Polyangiitis

Table 2. ANCA evaluation in non-vasculitis diseases

Non-vasculitis	ANCA n (%)		Positive ANCA n (%)		MPO positive n (number of tests)	PR3 positive n (number of tests)
	Negative	Positive	P ANCA	C ANCA		
Connective tissue disease (undiagnosed) N=146	136 (93.2)	10 (6.8)	7 (70)	3 (30)	1 (6)	0 (5)
Rheumatoid Arthritis N=144	62 (43.1)	82 (56.9)	66 (80.5)	16 (19.5)	3 (56)	2 (47)
Systemic Lupus Erythematosus N=64	34 (53.1)	30 (46.9)	29 (96.7)	1 (3.3)	1 (22)	0 (19)
Scleroderma N=29	25 (86.2)	4 (13.8)	2 (50)	2 (50)	0 (4)	0 (4)
Sjogren N=71	64 (90.1)	7 (9.9)	6 (85.7)	1 (14.3)	2 (5)	0 (4)
Familial Mediterranean Fever N=63	61 (96.8)	2 (3.2)	1 (50)	1 (50)	1 (2)	0 (1)
Sarcoidosis N=12	10 (83.3)	2 (16.7)	1 (50)	1 (50)	0 (2)	0 (2)
Interstitial lung disease N=113	92 (81.4)	21 (18.6)	18 (85.7)	3 (14.3)	2 (14)	1 (12)
Infection N=126	111 (88.1)	15 (11.9)	14 (93.3)	1 (6.7)	2 (13)	0 (10)
Malignancy N=116	105 (90.5)	11 (9.5)	7 (63.6)	4 (36.4)	0 (7)	1 (6)
Inflammatory bowel disease (undiagnosed) N=12	9 (75)	3 (25)	2 (66.7)	1 (33.3)	0 (1)	0 (1)
Ulcerative colitis N=10	7 (70)	3 (30)	1 (33.3)	2 (66.7)	0 (1)	1 (1)
Liver disease (undiagnosed) N=16	14 (87.5)	2 (12.5)	1 (50)	1 (50)	0 (2)	0 (2)
Autoimmune hepatitis N=1	0 (0)	1 (100)	0 (0)	1 (100)	0 (1)	0 (1)
Primary sclerosing cholangitis N=1	0 (0)	1 (100)	1 (100)	0 (0)	0 (1)	0 (0)
Demyelinating disease (undiagnosed) N=194	183 (94.3)	11 (5.7)	7 (63.6)	4 (36.4)	0 (10)	1 (10)
Multiple Sclerosis N=247	228 (92.3)	19 (7.7)	13 (68.4)	6 (31.6)	1 (15)	1 (13)
Chronic renal failure N=383	344 (89.8)	39 (0.2)	33 (84.6)	6 (15.4)	2 (39)	1 (34)
Cerebrovascular accident N=393	373 (94.9)	20 (5.1)	12 (60)	8 (40)	0 (19)	2 (16)
Other (unclassifiable diseases) N=2653	2577 (97.1)	77 (2.9)	56 (72.7)	21 (27.3)	5 (56)	0 (49)
Total N=4795	4435 (92.5)	360 (7.5)	277 (76.9)	83 (23.1)	20 (276)	10 (238)

Connective tissue disease was grouped into rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, Sjogren, Familial Mediterranean Fever (FMF), sarcoidosis and unidentified. Malignity diagnoses included myelodysplastic syndrome, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (KLL), chronic myeloid leukemia (KML), non-Hodgkin lymphoma, multiple myeloma, central nervous system lymphoma, Ewing sarcoma, Kaposi sarcoma, thymoma, dermal malignant neoplasm, pancreatic adenocarcinoma, pulmonary, renal, stomach, colon, bladder, ovary, vulva, cervical and prostate cancer (Table 2). When 422 ANCA-positive patients are evaluated, 137 (32.5%) of ANCA-positive non-vasculitis cases were followed-up with connective tissue disease, 21 (5.0%) with interstitial pulmonary disease, 19 (4.5%) with multiple sclerosis (MS), 39 (9.2%) with chronic renal failure (CRF), 20 (4.7%) with cerebrovascular accident, 15 (3.6%) with infection and 11 (2.6%) with malignancy.

AAV prevalence was found at 0.6% in 5107 patients subject to ANCA evaluation. 18 of AAV-diagnosed patients were women (54.5%) and 15 were men (45.5%). The age of AAV patients was statistically high compared to non-AAV patients (p=0.0001; non-AAV patients: 47.6±20.28, min-max: 3-94; AAV patients: 61.1±16.02 min-max: 21-86).

PR3-ANCA (68.8%) and MPO-ANCA (31.2%) were detected in GPA; MPO-ANCA (100%) in MPA; and MPO-ANCA (66.7%) and PR3-ANCA (33.3%) were detected in ANCA-associated vasculitis patients (Table 1).

ANCA-positivity was found at 16.7% for patients with IgA vasculitis, 18.6% for leukocytoclastic vasculitis, 56.9% for RA, 46.9% for SLE, 18.6% for interstitial pulmonary disease, 7.7% for MS, 10.2% for KBY, and 5.1% for SVO (Table 1, 2).

In vasculitis patients, P-ANCA was detected positive in 37 (59.7%) and C-ANCA in 25 (40.3%) patients; and in non-vasculitis patients, P-ANCA was found positive in 277 (76.9%) and C-ANCA in 83 (23.1%) patients. When the PR3-ANCA, MPO-ANCA patterns were evaluated for ANCA-positive patients MPO-ANCA was found in 16 of 62 vasculitis patients, PR3-ANCA in 13 vasculitis patients; further, of 360 patients with non-vasculitis diseases, 20 presented MPO-ANCA and 10 presented PR3-ANCA pattern (Table 1, 2).

Discussion

As seen in our study and previous ones, ANCA-positivity can be detected in ANCA-associated vasculitis and other vasculitis forms [5-8]. In ANCA-associated vasculitis, PR3-ANCA and MPO-ANCA positivity define different conditions. Patients with GPA are predominantly PR3-ANCA positive, whereas patients with MPA are predominantly MPO-ANCA positive. It is possible to classify patients with AAV according to the specificity of ANCA. In addition, ANCA's specificity predicts induction treatment responses, recurrence risk and differences in long-term prognosis [9]. In our study, PR3-ANCA was predominantly positive in patients with GPA, MPO-ANCA was predominantly positive in patients with MPA and in patients with vasculitis associated with renal-localized vasculitis.

Leukocytoclastic vasculitis (LCV) is a histopathological definition of a common small vessel vasculitis (SVV) form that can be found in various types of vasculitis that affect the skin and internal organs. Autoantibodies (anti-nuclear antibodies and ANCA) are routinely studied among the diagnostic tests [10]. In a study of the prognostic factors of the LVC, only 21% of patients were ANCA-positive, and P-ANCA pattern was found in all positive patients. Forty percent of these patients presented systemic involvement. In LVC, P-ANCA is not identified as a marker for systemic vasculitis [5]. In our study, only 18.6% of patients with LCV diagnosis were ANCA-positive. Respectively, 62.5% and 37.5% of ANCA-positive patients presented P-ANCA and C-ANCA patterns.

In a study that explores the clinical importance of ANCA positivity in patients with IgA vasculitis (Henoch-Schoenlein purpura), ANCA positivity was reported to be 5.8%. All ANCA-positive patients presented the MPO-ANCA profile. Pulmonary and nerve involvement were observed at a higher rate in ANCA-positive patients. There was no significant difference in terms of renal involvement [6]. In our study, HSP patients presented a higher rate of ANCA positivity. MPO and PR3 target antigens were not detected.

ANCA positivity is seen in non-vasculitis diseases as well. Some of these diseases include connective tissue diseases, idiopathic interstitial pneumonia, autoimmune liver diseases, inflammatory bowel diseases, anti-glomerular basal membrane (GBM) disease, infections, and malignancy [3]. In our study, ANCA-positivity was detected in non-vasculitis diseases as well.

In rheumatoid arthritis (RA) P-ANCA positivity varies between 16% and 50%. On the other hand, MPO-ANCA positivity is rarely found with antigen-specific immunoassay. The clinical value of P-ANCA is not definitive [3]. In our study, P-ANCA positivity was found at such a high rate of 85%. However, the MPO-ANCA pattern was detected in a small number.

In a study where the importance of ANCA is investigated in systemic lupus erythematosus patients, ANCA prevalence was reported as 29.6% compared to IIF. P-ANCA (89%) was detected as the most common pattern. Two patients showed positivity to MPO and PR3. No significant correlation was detected between P-ANCA/C-ANCA positivity and clinic [11]. In another study involving 74 SLE patients in Colombia, 60 (81.1%) of patients were reported ANCA-positive by the IIF method. Only one patient presented specificity for PR3-ANCA with ELISA [12]. In our study, ANCA prevalence was found in 64 SLE patients at 46.9%. Like in the two studies, MPO and PR3 were detected rarely in our study.

Interstitial pulmonary diseases (ILD) include a heterogeneous pulmonary disease group. An underlying connective tissue disease or vasculitis associated with RA or ANCA can cause ILD. The pulmonary findings of these diseases may be prior to the systemic onset. As clinical, radiological and broncho-alveolar lavage data for patients with interstitial lung disease appear similar in ANCA-positive and ANCA-negative patients at diagnosis, a systemic screening for ANCA seems reasonable. A P-ANCA screening can be useful [13]. In our study, the P-ANCA pattern was seen at a high rate (85.7%) in ANCA-positive patients diagnosed with ILD.

Different studies conducted with multiple sclerosis patients report ANCA-positive results [14-16]. In a study conducted with 176 MS patients whose autoantibody distribution was evaluated, only four patients presented ANCA positivity, and ANCA positivity was not associated with the clinic [14]. A total of 117 MS patients were evaluated in a study that explored the importance of ANCA in patients with the idiopathic inflammatory-demyelinating disease (IIDD); one patient was reported with the C-ANCA pattern, and two patients with the P-ANCA pattern [15]. The research shows a high rate of ANCA-positivity according to the MS form. 46.2% of 13 Japanese patients with optical-spinal MS forms were reported to be P-ANCA-positive [16]. In our study with 247 MS-diagnosed patients, 19 were ANCA-positive. Thirteen of them were P-ANCA and 6 of them C-ANCA. ANCA positivity was detected at a higher rate than the previous studies [14, 15]. Since the study is retrospective, it was not possible to evaluate which form of MS the patients were.

Chronic renal failure etiology is very diverse. In a recent study that researched ANCA positivity in non-vasculitis diseases associated with ANCA, chronic renal disease has been reported to be the most common disease group [17]. In the present study, chronic renal failure was found as the most common disease among non-vasculitis diseases after connective tissue diseases.

Studies evaluating ANCA usually focus on a single disease, with the exception of ANCA-related vasculitis. There are a limited number of studies in which many diseases were evaluated simultaneously. In diseases other than ANCA-related vasculitis, ANCA positivity was most frequently observed in unspecified vasculitis among rheumatic and autoimmune diseases, when cardiovascular and cerebrovascular diseases were evaluated, most frequently in atherosclerotic heart disease, and in diseases related to liver, kidney and lungs, it was most frequently observed in chronic kidney disease [17]. In another study evaluating the test and diagnostic indications in patients with ANCA positivity, the cause could not be determined in 23% of AAV, 25% of unspecified vasculitis, 48% of inflammatory condition and 4% of patients [18].

The present study has considered the diagnoses of diseases discussed as part of the 2020 international consensus about ANCA testing, and many diseases were evaluated in

the same study concerning the ANCA testing. The limitations of the present study include, above all, its retrospective design, followed by its single-centered character.

As a result, cases of vasculitis were detected ANCA-positive at a higher rate than non-vasculitis diseases. P-ANCA was the most common pattern observed in both groups. In non-vasculitis diseases, the target antigen MPO-ANCA and PR3-ANCA positivity were rare compared to vasculitis cases. Among the ANCA-positive patients, the most common non-vasculitis disease was connective tissue disease, chronic renal failure, and interstitial pulmonary disease. ANCA testing can be used to support diagnosis and to assist in differential diagnosis in vasculitis and non-vasculitis diseases.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

S.Z.O., B.O. and M.D. constructed the main idea and hypothesis of the study. S.Z.O., B.O. and M.D. developed the theory and arranged/ edited the material and method section. S.Z.O., B.O., M.D. and C.E. has/have done the evaluation of the data in the Results section. Discussion section of the article written by S.Z.O.

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