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Review Article

Classification of Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic vasculitides, that are characterized by inflammation in the small vessels, ranging from capillaries to arterioles or venules. AAV is divided into three variants based on the clinical manifestations and histological findings such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA). MPA often induces rapid progressive necrotising glomerulonephritis, and occasionally induces diffuse alveolar hemorrhage. In contrast, GPA preferentially affects the respiratory tracts from the bronchus to the nasal cavity. GPA can also involve the kidneys, but the frequency of renal involvement is less than MPA. EGPA is based on allergic components such as asthma, peripheral eosinophilia, migratory eosinophilic pneumonia and eosinophil infiltration. Since 1982, when the association between ANCA and systemic vasculitis was first reported, several classification criteria for AAV have been proposed. This review describes the classification criteria for and nomenclature of AAV from the 1990 American College of Rheumatology (ACR) classification criteria to the 2012 revised Chapel Hill consensus conference (CHCC) nomenclature of Vasculitides. New classification trials for AAV such as AAV based on the ANCA-types (myeloperoxidase-ANCA vasculitis, proteinase 3-ANCA vasculitis and ANCA negative vasculitis) and the ACR/European League Against Rheumatism (EULAR) 2017 provisional classification criteria for GPA were also introduced. In addition, the histopathological classification of ANCA-associated glomerulonephritis and the revised 2017 international consensus on testing of ANCAs in GPA and MPA are also discussed. **(J Rheum Dis 2019;26:156-164)**

Key Words. Antineutrophil cytoplasmic antibody, Vasculitis, Classification

INTRODUCTION

Systemic vasculitides are generally categorized based on the size of the vessels affected. Large vessel vasculitis includes Takayasu arteritis and giant cell arteritis and medium vessel vasculitis consists of polyarteritis nodosa (PAN) and Kawasaki disease. Small vessel vasculitis is divided into two groups based on immune deposits in the affected organ-tissues such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune complex small vessel vasculitis. Immune complex small vessel vasculitis includes cryoglobulinemic vasculitis, immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura, HSP) and hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis). Capillaritis in the lungs and kidneys, which manifests as diffuse alveolar hemorrhage or glomerulonephritis, rarely occurs in medium vessel vasculitis such as PAN. Behçet's disease can involve small, medium and large vessels, so it is called variable vessel vasculitis [1,2]. AAV is a group of systemic vasculitides, which is characterized by inflammation in the small vessels ranging from capillaries to arterioles or venules. The histological features of AAV are mainly necrotizing vasculitis with few or no immune deposits on the affected organs [3,4]. AAV is also distributed to three variants based on the clinical manifestations and histological findings, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic

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GPA (EGPA) [1,5]. GPA, which was first introduced and formerly known as Wegener's granulomatosis (WG) [6], describes the pathological features, so GPA is recommended name. EGPA and Churg-Strauss syndrome (CSS) are use identically [1]. MPA often induces rapid progressive necrotizing glomerulonephritis, and occasionally induces diffuse alveolar hemorrhage [7]. In contrast, GPA preferentially affects the respiratory tract from the bronchus to the nasal cavity. GPA can also involve the kidneys, even though the frequency of renal involvement is less than MPA. Among the three AAV variants, cartilaginous involvement is observed mainly in GPA and is defined as inflamed ear or nose cartilage or hoarse voice/stridor, endobronchial involvement or saddle nose deformity [8]. EGPA is based on allergic components, such as asthma, peripheral eosinophilia, migratory eosinophilic pneumonia and eosinophil infiltration [9,10].

Thus far, there have been many efforts to develop diagnostic methods to classify and confirm AAV. ANCA appears to be closely related to AAV, but, not all AAV patients have ANCA and the rate of ANCA detection is lower than expected: myeloperoxidase (MPO)-ANCA is detected in 30%～80% of MPA patients, 0%～10% of GPA patients and 32%～92% of EGPA patients, whereas, proteinase 3 (PR3)-ANCA is detected in 10%～20% of MPA patients, 40%～95% of GPA patients and 0%～3.2% of EGPA patients [11]. Moreover, there is currently no method that is conclusive in helping to classify AAV. For these reasons, the various clinical classification criteria have been developed, proposed and validated. The classification criteria are different from the diagnostic criteria. The former is defined as observations that classify a specific patient into a standardized category for study, whereas the latter is defined as observations that demonstrate or confidently predict the presence of the defining features of the disease in a specific patient. This review introduces the classification criteria for AAV proposed to date.

MAIN SUBJECTS

1990 American College of Rheumatology (ACR) classification criteria and 1994 Chapel Hill consensus conference (CHCC) nomenclature of systemic vasculitides

The 1990 ACR classification criteria (the 1990 ACR cri-

Table 1. The 1990 American College of Rheumatology classification criteria for antineutrophil cytoplasmic antibody-associated vasculitis and polyarteritis nodosa

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Granulomatosis with polyangiitis (Wegener's granulomatosis)	Microscopic polyangiitis	Polyarteritis nodosa
1) Asthma (histology) 2) Peripheral eosinophilia (>10% of peripheral blood) 3) Mono or polyneuropathy 4) Pulmonary infiltrates (non-fixed) 5) Paranasal sinus abnormality 6) Extravascular eosinophils on histology	1) Nasal or oral inflammation 2) Chest radiograph (nodules, fixed infiltrates or cavities) 3) Micro-haematuria or red blood cell casts in urine sediment 4) Granulomatous inflammation on histology	None	1) Weight loss >4 kg 2) Livedo reticularis 3) Testicular pain/tenderness 4) Myalgia, weakness or leg tenderness 5) Mono or polyneuropathy 6) Diastolic blood pressure >90 mmHg 7) Elevation of blood urea nitrogen >40 mg/dL or creatinine >1.5 mg/dL 8) Presence of hepatitis B surface antigen or antibody in serum 9) Arteriogram showing aneurysms or occlusions of the visceral arteries 10) Biopsy of small or medium-sized artery containing polymorphonuclear cells
4 items or greater are met Sensitivity 85.0% Specificity 99.7%	2 items or greater are met Sensitivity 88.2% Specificity 92.0%		3 items or greater are met Sensitivity 82.2% Specificity 86.6%

teria) provide the classification criteria for EGPA, GPA and PAN but not MPA [12-14]. The 1990 ACR criteria for AAV and PAN are summarized in Table 1. The 1990 ACR criteria for EGPA consist of six items as follows: i) asthma (or history of asthma), ii) peripheral eosinophilia, iii) mono or polyneuropathy, iv) non-fixed pulmonary infiltrates, v) abnormality of paranasal sinus, and vi) extravascular eosinophil infiltration on histology. EGPA can be classified firmly when four items or greater are met [13]. The 1990 ACR criteria for GPA comprise 4 items as follows: i) nasal or oral inflammation, ii) nodular, fixed or cavitary pulmonary involvement, iii) urinary abnormality (microhaematuria or red blood cell casts), iv) granulomatous inflammation on histology. GPA can be classified when two items or greater are satisfied [12]. The 1990 ACR criteria had several limitations. The 1990 ACR criteria provide those for PAN rather than MPA [14]. They did not include other vasculitides, which should be differentiated from AAV, such as primary central nervous system vasculitis, Cogan's syndrome and cryoglobulinemic vasculitis. In addition, they could not distinguish vasculitis from vasculitis-mimicking diseases.

In 1994, the CHCC nomenclature of systemic vasculitides (the 1994 CHCC definitions) was proposed. The 1994 CHCC definitions provided standardized nomenclature of vasculitides and subgroups using a general and widely used terminology. Unlike the 1990 ACR criteria, the 1994 CHCC definitions defined PAN and MPA separately. They described PAN as necrotizing inflammation of the medium-sized or small arteries without glomerulonephritis or vasculitis in the arterioles, capillaries or venules. In contrast, they described MPA as necrotizing vasculitis, with few or no immune deposits affecting the small vessels (capillaries, venules and arterioles). In addition, they added a comment that MPA may involve the small and medium-sized arteries and MPA exhibits commonly present glomerulonephritis and often pulmonary capillaritis [2]. In other words, PAN and MPA might be a common range in that their histological feature is necrotizing vasculitis and both can partially share the size of the vessels affected. On the other hand, clinical manifestations due to capillaritis such as glomerulonephritis and diffuse alveolar hemorrhage may be critical clues to suggest MPA. The 1994 CHCC definitions also had several limitations. They included ANCA tests, which were not included in the 1990 ACR criteria, but they did not provide a predictive value of ANCA to differentiate AAV from other vasculitides. The 1994 CHCC definitions were based primarily on the histological features. Hence, they could not be applied to patients who did not undergo biopsy. Moreover, the rate of the reclassification in MPA and GPA patients was not high.

2007 European Medicine Agency (EMA) algorithm for the classification of AAV and PAN

In 2007, a new algorithm for the classification of AAV and PAN was proposed by the EMA. There are three requirements for initiating the 2007 EMA algorithm for the classification of AAV and PAN (the 2007 EMA algorithm). The first requirement is the follow-up duration for 3 months or greater. The second requirement is the age of onset over 16 years old. The third requirement should meet all three of the following: A) symptoms and signs compatible with AAV or PAN; B) at least one of the following: i) histological proof of vasculitis, ii) ANCA positivity, and iii) specific investigations strongly suggestive of vasculitis or granuloma such as neurophysiology, angiography or magnetic resonance imaging. Both IgA deposits and anti-glomerular basement membrane (GBM) antibodies may occur concurrently with AAV, iv) eosinophilia ($>10\%$ or $>1.5\times10^9$/L); C) no other diagnosis to account for the symptoms and signs such as malignancy, infection (hepatitis B and C virus, tuberculosis), drugs (hydralazine, propylthiouracil, cocaine), other vasculitides and vasculitis mimics [5]. According to the third requirement, HSP and anti-GBM disease can occur simultaneously with AAV, but also play a role in excluding AAV. Therefore, a precise diagnosis of AAV must depend on the physicians' decisions.

In addition, the 2007 EMA algorithm suggests surrogate markers for WG (GPA), which involve lower airways, including i) X-ray evidence of fixed pulmonary infiltrates, nodules or cavitations present for >1 month and ii) bronchial stenosis. Surrogate markers involving the upper airways include i) bloody nasal discharge and crusting for >1 month or nasal ulceration, ii) chronic sinusitis, otitis media or mastoiditis for >3 months, iii) retro-orbital mass or inflammation (pseudotumour), iv) subglottic stenosis and v) saddle nose deformity/destructive sinonasal disease. Among several surrogate markers for GPA, only one surrogate marker is necessary. The 2007 EMA algorithm also provides surrogate markers for renal vasculitis (glomerulonephritis), which are either hematuria associated with red cell casts (or $>10\%$ dysmorphic erythrocytes) or 2+hematuria and 2+proteinuria on urinalysis [5].

The 2007 EMA algorithm for AAV and PAN was modified and depicted in Figure 1.

Once a patient fulfils three entry requirements, the 2007 EMA algorithm can be applied. The first step is to apply the 1990 ACR criteria for CSS (EGPA) to a patient. If a patient meets the 1990 ACR criteria for CSS (EGPA), a patient can be classified as EGPA and no further application is required. A patient can be classified as GPA by the four conditions as follows: i) when a patient fulfils the 1990 ACR criteria for WG (GPA); ii) when a patient exhibits a histology compatible with WG (the 1994 CHCC definition); iii) when a patient exhibits a histology compatible with MPA (the 1994 CHCC definition) and WG (GPA) surrogate markers, and iv) when a patient has WG (GPA) surrogate markers and ANCA in the absence of histology [5]. After the 1994 CHCC definitions were proposed, the first condition for the classification of GPA was considered controversial because there might be a range of confounding situations to mimic GPA [1]. A patient can be classified as MPA by the two conditions after excluding EGPA and GPA as follows: i) when a patient exhibits the clinical features and histology compatible with MPA in the absence of WG (GPA) surrogate markers and ii) when a patient has ANCA and renal vasculitis in the absence of histology or WG (GPA) surrogate markers [5]. A patient is rarely diagnosed with AAV if a patient cannot be classified as EGPA, GPA and MPA. A previous study, which validated the clinical implications of the 2007 EMA algorithm using the 2012 CHCC criteria, reported that the 2012 CHCC definitions resulted in no change to the performance of the EMA algorithm for the classification of AAV [15].

Revised 2012 CHCC nomenclature of vasculitides

The revised CHCC definitions were proposed in 2012. These definitions divided small vessel vasculitis into two groups such as AAV and immune complex small vessel vasculitis. Accordingly, the 2012 definitions officially used ANCA to define the categories of small vessel vasculitis for the first time. Based on the 2012 CHCC definitions, AAV is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting the

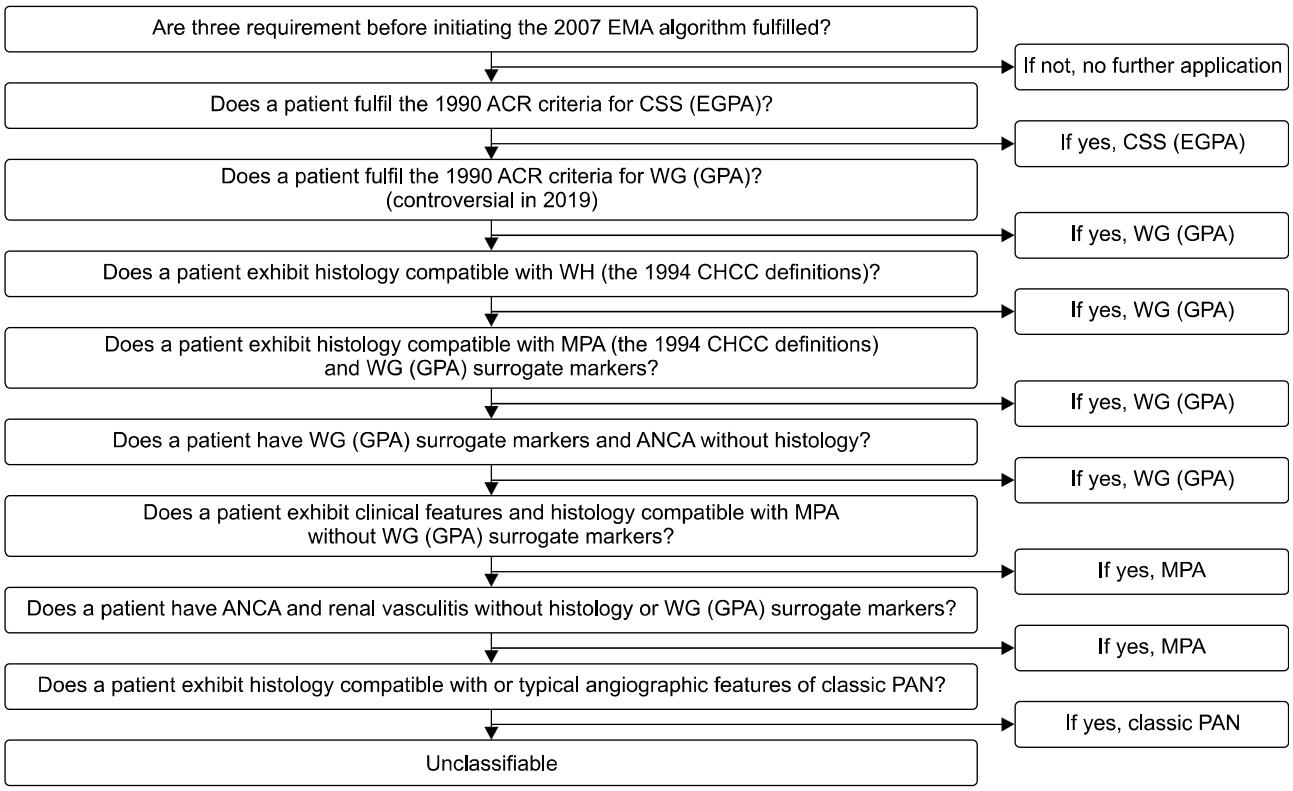

Figure 1. The 2007 EMA algorithm for AAV and PAN. EMA: the European Medicine Agency, AAV: associated vasculitis, PAN: classic polyarteritis nodosa, ACR: the American College of Rheumatology, CSS: Churg-Strauss syndrome, EGPA: eosinophilic granulomatosis with polyangiitis, WG: Wegener's granulomatosis, CHCC: Chapel Hill consensus conference, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, ANCA: antineutrophil cytoplasmic antibody.

small vessels. AAV may be associated with ANCA but this association is not obligatory. Furthermore, the 2012 CHCC definitions suggest a prefix indicating ANCA reactivity such as MPO-ANCA, PR3-ANCA, and ANCA-negative, which will be discussed later in this article [1]. The 2012 CHCC definitions for MPA, GPA and EGPA are cited and summarized in Table 2. EGPA is described as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting the small to medium vessels and is associated with asthma and eosinophilia. GPA is described as necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly the small to medium vessels. MPA is described as necrotizing vasculitis, with few or no immune deposits, predominantly affecting the small vessels, such as capillaries, venules, or arterioles without granulomatous inflammation. Glomerulonephritis occurs very often in MPA, commonly in GPA and occasionally in EGPA. Pulmonary capillaritis often occurs in MPA but may occasionally be observed in GPA and EGPA patients [1].

Modified classification criteria

The 2007 EMA algorithm for AAV and PAN was modified by the 2012 CHCC criteria and preliminary modified classification criteria for AAV in Korean patients were developed, as shown in Figure 2. These criteria are based on the 2007 EMA algorithm but the first condition of the 2007 EMA algorithm for GPA (Does a patient fulfil the 1990 ACR criteria for WG [GPA]?) was deleted. In contrast, a condition is added in that no glomerulonephritis can occur in PAN, and that PAN is rarely associated with ANCA positivity. The first condition of the 2007 EMA algorithm for GPA (Does a patient fulfil the 1990 ACR criteria for WG [GPA]?) was deleted. The same surrogate markers suggesting WG (GPA) with those of the 2007 EMA algorithm was used. Histopathological confirmation is the most critical for the classification of AAV, even though the absence of histology was accepted when other strongly suggestive clinical and laboratory data are present such as the surrogate markers for GPA, ANCA positivity and urinalysis for hematuria and proteinuria. Therefore, if possible, physicians should perform a biopsy of the affected organ-tissues, such as the kidneys, lungs, nerves and nasal sinus, including nasopharyngeal masses [16].

New classification criteria for AAV

A new trial for reclassifying AAV into three variants based on the ANCA positivity or negativity and its types, such as MPO-ANCA, PR3-ANCA and ANCA negative vasculitis was reported recently [17]. The authors explained the background of this study for three reasons. First, compared to EGPA and GPA, the conditions for MPA of the 2007 EMA algorithm and the 2012 CHCC definitions are unclear [1,5,15,18]. Second, neither MPO-ANCA nor PR3-ANCA are not emphasized despite the origin of the name of AAV [1]. In addition, even the 2017 EMA algorithm mentions ANCA positivity rather than MPO-ANCA positivity or PR3-ANCA positivity [5]. Third, recent studies have supported the distinct entities among MPO-ANCA, PR3-ANCA, and ANCA negative vasculitis [16]. This concept of a new classification method was determined by the different genetic background between the two epitopes. The chromosomal locus of

Table 2. The revised 2012 Chapel Hill consensus conference nomenclature of vasculitides

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Granulomatosis with polyangiitis (Wegener's granulomatosis)	Microscopic polyangiitis
Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

ANCA: antineutrophil cytoplasmic antibody.

Conditions	ACR for EGPA (1990 ACR)	Histology compatible with 2012 CHCC definition for GPA	Histology compatible with 2012 CHCC definition for MPA and GPA surrogate markers	No histology and GPA surrogate markers and PR3- or MPO-ANCA positivity	Clinical and histology compatible with 2012 CHCC definition for MPA and no GPA surrogate markers	No histology and No GPA surrogate markers and PR3- or MPO-ANCA positivity and renalvasculitis	Histology compatible with 2012 CHCC definition for cPAN or typical angiographic features of cPAN
Classified as	EGPA	GPA	GPA	GPA	MPA	MPA	cPAN
Comments	Necrotizing granuloma with eosinophil infiltrate 1) History of asthma 2) Eosinophil >10% 3) Mono- or poly-neuropathy 4) Migratory non-fixed pulmonary infiltrates 5) Paranasal sinusitis 6) Extravasation of eosinophil on histology (4 of 6)	Necrotizing granuloma without eosinophil infiltrate	Necrotizing vasculitis without granuloma without eosinophil infiltrate with few or no immune deposit Upper respiratory or lower respiratory surrogate markers for GPA	Upper respiratory or lower respiratory surrogate markers for GPA	Necrotizing vasculitis without granuloma without eosinophil infiltrate with few or no immune deposit		No GN Rare ANCA

Figure 2. The modified classification criteria for AAV and PAN in Korean patients. These criteria are based on the 2007 EMA algorithm but the first condition of the 2007 EMA algorithm for GPA (Does a patient fulfil the 1990 ACR criteria for WG [GPA]?) was deleted. In contrast, a condition is added in that no glomerulonephritis can occur in PAN, and that PAN is rarely associated with ANCA positivity. AAV: antineutrophil cytoplasmic antibody-associated vasculitis, PAN: classic polyarteritis nodosa, EMA: the European Medicine Agency, GPA: granulomatosis with polyangiitis, ACR: the American College of Rheumatology, WG: Wegener's granulomatosis, ANCA: antineutrophil cytoplasmic antibody, EGPA: eosinophilic granulomatosis with polyangiitis, CHCC: Chapel Hill consensus conference, MPA: microscopic polyangiitis, PR3: proteinase 3, MPO: myeloperoxidase, GN: glomerulonephritis.

PR3 is 17q23.1, whereas that of MPO is 19p13.3 [19-21]. PR3 is expressed on the membrane surface of resting neutrophils whereas MPO is not expressed [22,23]. Moreover, PR3-ANCA consists mostly of IgG and may induce the weak activation of primed neutrophils in vitro, whereas MPO-ANCA is composed of only IgG and may induce relatively strong activation [16]. In addition, MPA patients can exhibit different clinical manifestations at diagnosis or prognosis during follow-up according to MPO-ANCA positivity, PR3-ANCA positivity or ANCA negativity. For example, rituximab is more effective than cyclophosphamide in patients with PR3-ANCA whereas both rituximab and cyclophosphamide are similarly effective in patients with MPO-ANCA. In addition, patients with PR3-ANCA are at higher risk of relapse than patients with MPO-ANCA [24].

On the other hand, the diagnostic and classification criteria for primary systemic vasculitis (DCVAS) and collaborators recently proposed the ACR/European League Against Rheumatism (EULAR) 2017 provisional classification criteria for GPA. These criteria include nine items: five items are clinical variables and four items are test-variables. Different weights were assigned to each item. The score assigned to cytoplasmic (C)-ANCA or PR3-ANCA was the highest among the items. In particular, nasal polyps and eosinophilia >10%, which favor EGPA, are negative contributors to the diagnosis of GPA. When a patient obtains a total score of five or greater, he/she can be classified as GPA (presented at 2016 ACR session: New Classification Criteria for ANCA-associated Vasculitis: implications for clinical practice) (Table 3). On the other hand, the 2017 provisional criteria have several limitations in that they did not include any items of kidney involvement for GPA or fixed lung infiltrates. Furthermore, PR3-ANCA positivity might be overestimated compared to the 1990 ACR criteria or the 2007 EMA algorithm modified by the 2012 CHCC definitions. Therefore, the weight of PR3-ANCA positivity should be readjusted in the near future [25].

Table 3. The 2017 Provisional ACR/EULAR classification criteria for GPA

	Items									
	Score for the ACR/EULAR 2017 provisional classification criteria for GPA	Bloody nasal discharge, ulcers, crusting or sinonasal congestion	Nasal polyps	Hearing loss or reduction	Cartilaginous involvement	Red or painful eyes	C-ANCA or PR3-ANCA	Eosinophil count ≥1 ($\times 10^9$/L)	Nodule, mass or cavitation on chest imaging	Granuloma on biopsy
Score	Sum ≥5	3	−4	1	2	1	5	−3	2	3

When a patient gets the total score of 5 or greater, he/she can be classified as GPA. ACR: the American College of Rheumatology, EULAR: the European League Against Rheumatism, GPA: granulomatosis, C-ANCA: cytoplasmic-antineutrophil cytoplasmic antibody, PR3-ANCA; proteinase 3-ANCA.

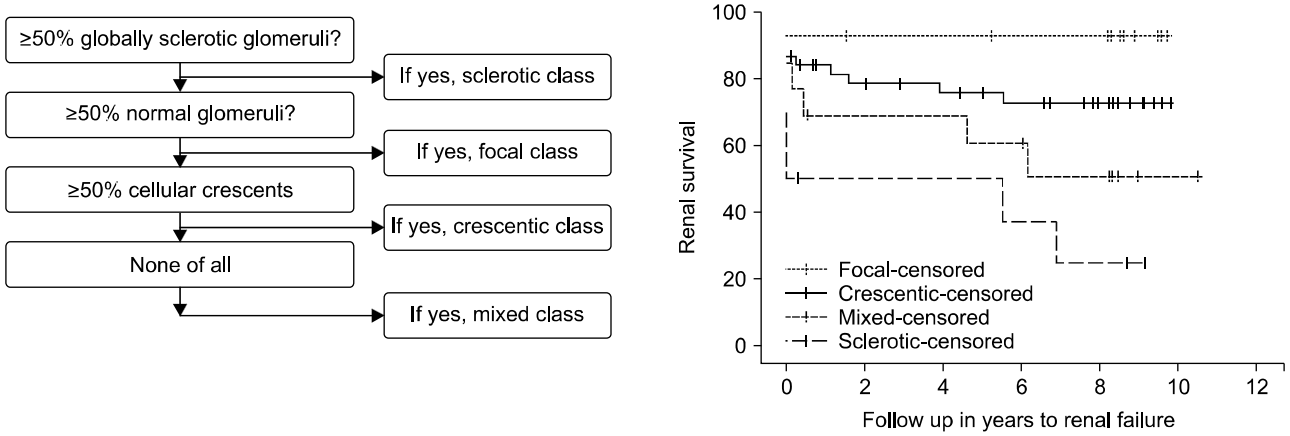

Figure 3. Histopathological classification of antineutrophil cytoplasmic antibody-associated glomerulonephritis.

Histopathological classification of ANCA-associated glomerulonephritis

When AAV predominantly involves the kidneys more frequently than the other major organs, it is referred to as ANCA-associated renal vasculitis. In particular, MPA and GPA often induce acute and chronic glomerulonephritis and tubular inflammation, which are important risk factors for an impaired renal function during follow-up [11]. Vascular lesions and damages are also observed in kidney-tissues, such as arteriosclerosis, but they have been considered not to commonly provoke renal impairment. ANCA-associated glomerulonephritis is critical for the classification of AAV via renal histopathology, which is characterized by necrotizing and crescentic glomerulonephritis with little or no glomerular staining for immunoglobulins or immune deposits (so-called pauci-immune staining pattern) [4]. Several definitions related to the histopathology of AAV-associated glomerulonephritis are as follows: i) normal glomeruli are defined as glomeruli without vasculitic lesions or global sclerosis with the possibility of subtle changes as a result of ischemia or a minimum number of inflammatory cells, ii) cellular crescents are defined as purely cellular lesions or with cellular components, iii) fibrous crescents are defined as fibrotic (sclerotic) lesion with fibroblasts filling Bowman's space, and iv) global glomerulosclerosis is defined as > 80% of the glomerulus scleroses. The classification scheme for ANCA-associated glomerulonephritis classifies patients with ANCA-associated glomerulonephritis into four classes: focal (≥50% normal glomeruli), crescentic (≥50% cellular crescents), mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli) and sclerotic (≥50% globally sclerotic glomeruli). The histopathological findings are generally scored in the following order: globally sclerotic glomeruli, normal glomeruli, and cellular crescents (Figure 3) [3,26]. The histopathological classification of ANCA-associated glomerulonephritis has an important influence on the renal outcomes [27]. The incidence rates of estimated glomerular filtration rate <15 or on dialysis within the first 1

year of focal, crescentic, mixed and sclerotic are 0%, 15%, 25%, and 31%, respectively (Figure 3) [3].

Revised 2017 international consensus on testing of ANCAs in GPA and MPA

Screening tests for ANCAs are commonly performed for the classification of GPA and MPA in suspicious patients in real clinical settings. The association between ANCA and systemic vasculitis was first reported in 1982 [28], and the first observation of C-ANCA in GPA patients was made in 1985 [29]. In 1988 and 1989, MPO and PR3 were identified as autoantigens of ANCAs and P-ANCA was detected in GPA patients [30,31]. The 1999 international consensus statement on the testing and reporting of ANCA recommended that indirect immunofluorescence (IIF) should be performed as an initial screening method to detect ANCAs in patients suspected of systemic vasculitis. When ANCAs are detected, it was recommended that the same blood samples should be tested by immunoassays for the presence of antibodies specific to MPO and PR3 [32]. The immunoassay technique for detecting antibodies against MPO and PR3 has been improved and an assay setup has advanced over the past 15 years: capture-based assay as the second generation and anchor-based assay as the third generation. The currently available assays for MPO-ANCA and PR3-ANCA are highly sensitive and specific for the classification of GPA and MPA (high-quality immunoassays) [33]. Therefore, the role of IIF at the initial diagnostic tests for ANCAs is questioned.

In 2017, the revised international consensus on the testing of ANCAs in GPA and MPA was proposed [34] based on a large multi-centric study to compare the value between IIF and immunoassays for ANCA detection, which confirmed that the diagnosis efficiency of the antigen-specific immunoassay is equal to or even exceeds that of IIF [35]. The 2017 revised consensus provided six recommendations as follows: Recommendation 1) a gating policy for requesting an ANCA test if advisable and adherence to the clinical guidelines for ANCA testing is recommended. The clinical guidelines include glomerulonephritis, diffuse alveolar hemorrhage, skin vasculitis and mononeuritis multiplex together with the surrogate markers for GPA in the 2017 EMA algorithm, Recommendation 2) high-quality antigen-specific assays for PR3-ANCA and MPO-ANCA should be used as the primary screening method for ANCA, Recommendation 3) if the results for both PR3-ANCAs and MPO-ANCAs are negative, and there is still a strong suspicion of small-vessel vasculitis, then the use of other immunoassays and/or indirect IIF, or referral to an experienced laboratory is recommended. Performing a second assay or IIF can also marginally increase the specificity in cases of low-positive test results, Recommendation 4) a diagnosis of ANCA-AAV cannot be excluded based on negative PR3 ANCA and MPO-ANCA results, Recommendation 5) a positive PR3 ANCA and/or MPO-ANCA result only contributes to the diagnostic work up for AAV and is not diagnostic in itself; Recommendation 6) taking the antibody levels into account improves the clinical interpretation [34].

CONCLUSION

This review introduced the classification criteria for AAV, which have been proposed since 1990 and described efforts that have been made to overcome their limitations to date. The accurate methods or criteria for the classification of AAV are essential because the early classification of AAV can make it possible to expect a better prognosis by initiating treatment at the appropriate time. On the other hand, there are no current decisively diagnostic methods or criteria for the classification of AAV currently available. Future studies regarding novel serum biomarkers and epigenetic information for both the classification of AAV and predicting the prognosis will reduce the time of an accurate diagnosis of AAV.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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