

# Cardiac manifestations in antineutrophil cytoplasmic autoantibody (ANCA) — associated vasculitides

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## INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA) — associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA, “Wegener’s granulomatosis”), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) (Fig. 1) [1]. ANCA-associated vasculitis usually presents with life-threatening kidney failure or pulmonary haemorrhage, has a mortality rate of 28% at five years, and contributes to increased mortality and morbidity of these patients [2]. ANCAs with specificity for proteinase-3 (PR3) or myeloperoxidase are the hallmarks of AAV and play an important role in disease progression. ANCA-associated vasculitides share many common features. However, granulomatous destruction of the respiratory tract is more common in GPA, MPA uncommonly involves the upper airways or the eyes, whereas eosinophilia and asthma support the diagnosis of EGPA [3]. Allenbach et al. [4] in a large cohort of 1130 patients

found that patients with AAV had an increased risk of venous thrombo-embolic events, such as deep venous thrombosis and/or pulmonary embolism, especially during the active phases of the disease.

There have been several attempts to standardise the classification and diagnostic criteria for small-vessel vasculitis. The International Chapel Hill Consensus Conference (CHCC) criteria, which were revised in 2012, are the mostly commonly cited. GPA, MPA, and EGPA were distinguished from other systemic small-vessel vasculitides by the absence of immune deposits [5]. Definitions for vasculitides are presented in Table 1.

Prior to effective treatment, ANCA-associated vasculitides had a mortality of 93% within two years, mainly due to respiratory or renal failure. The introduction of glucocorticoids and cyclophosphamide, together with adjunctive therapies such as anti-hypertensive drugs and renal replacement therapy, has changed survival — with five-year survival rates now approaching 80% [6].

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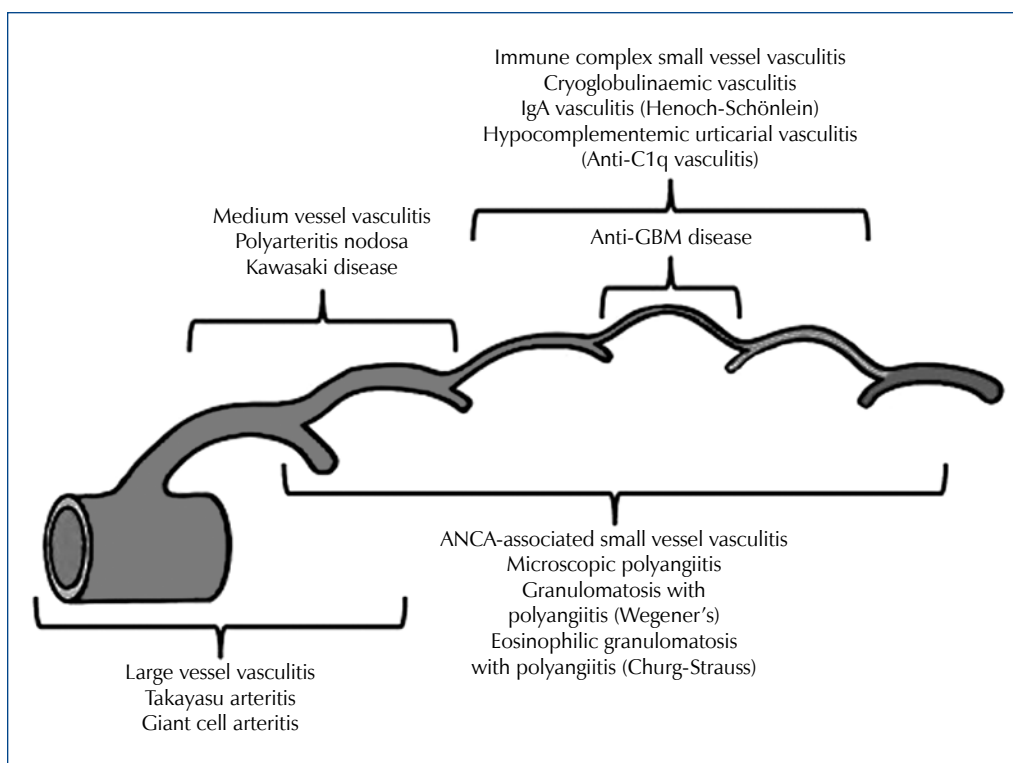
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**Figure 1.** Types of vessels involved in different forms of vasculitis; ANCA — antineutrophil cytoplasmic autoantibody; GMB — antiglomerular basement membrane

### CARDIAC MANIFESTATION IN GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis is one of the most common forms of systemic vasculitis, with a reported annual incidence of 10 cases per million [7]. Cardiac involvement in GPA occurs in 6% to 44% of cases [8, 9] and is secondary to necrotising vasculitis with granulomatous infiltrates.

The literature concerning cardiac involvement is limited. The few case reports and general reviews show that the two most common cardiac manifestations are pericarditis and coronary arteritis (50% of cases), but myocarditis, endocarditis, and conduction system disturbances are also described [10–13].

In two European cohort studies cardiovascular involvement in GPA patients was an independent risk factor for disease relapse and treatment resistance [14, 15]. However, in North America cohort cardiac involvement was not associated with a higher rate of mortality or relapse of vasculitis, but the frequency of cardiac involvement was much lower in this group than in European cohorts [16].

The overall mortality rate of GPA with cardiac involvement has been reported to be between 15% and 45% [17]. Estimates of the frequency of cardiac involvement in GPA vary widely, with a North American study reporting a rate of 33.3% and no association with a higher rate of relapse or premature death [16], while a European study reported cardiac involve-

ment in 46% of GPA patients assessed with electrocardiography and echocardiography, along with increased all-cause and cardiovascular mortality [18].

Pericarditis is the most common cardiac manifestation, accounting for about 50% of cases. It is usually asymptomatic, or may be manifested by chest pain or dyspnea [8–10]. Pericardial effusion can be due to the disease itself or due to uraemia in cases of renal failure [19, 20]. In most cases pericardial effusion is mild and clinically irrelevant, but in some cases it may lead to excessive effusion and tamponade [19, 20].

Coronary artery involvement is rare and is characterised by coronary arteritis and subsequent coronary artery thromboembolism [21]. Magnetic resonance imaging (MRI) study of coronary arteries in GPA patients revealed that in some patients coronary arteries dilatation can be observed [22]. Morbini et al. [23] report an extreme example of an elderly female with intimal inflammation in multiple sites of a coronary tree with and without atherosclerosis which triggered coronary thrombosis. She died after cardiac arrest from a clinically unrecognised systemic autoimmune-inflammatory disorder with necrotising arteritis. Autopsy showed findings typical of GPA and systemic arteritis with fibrinoid necrosis. Although there were no clinical signs of cardiac involvement, the coronary arteries showed inflammation associated with multiple thrombi [23]. The ischaemia in GPA patients may be due to the involvement of the small vessels secondary to the

**Table 1.** Definitions for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

<b>Small-vessel vasculitis</b>	Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries and veins may be affected.
<b>Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV)</b>	Necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g. MPO-ANCA, PR3-ANCA, ANCA-negative.
Microscopic polyangiitis (MPA)	Necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, or arterioles). Necrotising arteritis involving small and medium arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (GPA) (Wegener's)	Necrotising granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotising vasculitis affecting predominantly small to medium vessels (e.g. capillaries, venules, arterioles, arteries, and veins). Necrotising glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss)	Eosinophil-rich and necrotising granulomatous inflammation often involving the respiratory tract, and necrotising vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. Antineutrophil cytoplasmic autoantibody is more frequent when glomerulonephritis is present.
<b>Immune complex vasculitis</b>	Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent.
Antiglomerular basement membrane (anti-GBM disease)	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary haemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.
Cryoglobulinaemic vasculitis (CV)	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved.
IgA vasculitis (IgAV) (Henoch-Schonlein)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.
Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

vasculitic process rather than the atherosclerosis as it responds to immunosuppressive therapy with reversal of ischaemic changes [24]. There are several cases that described patients with GPA and myocardial infarction (MI) [25–28]. In the Danish National Hospital register patients had an increased rate of MI within five years of diagnosis of GPA when compared to the general population [29].

Frequent cardiac manifestations in GPA are cardiac arrhythmias, typically supraventricular tachyarrhythmias and conduction abnormalities [30, 31]. Ohkawa et al. [32] reported a case of generalised GPA with extensive cardiac involvement at autopsy. Necrotising angiitis and severe granulomatous inflammatory foci affected the common bundle of His and right bundle branch in addition to the myocardium [32]. Suleymenlar et al. [33] report a case of patients with completed heart block due to GPA. Inflammation near the

atrioventricular (AV) node was seen on computerised tomography (CT) and cardiac MRI, but also was confirmed by a myocardial perfusion scan with gallium [33].

Cardiac valvular involvement is an uncommon manifestation of GPA, but can be a potentially fatal complication of GPA. The most frequent valvular presentation is aortic regurgitation and the second is mitral insufficiency. Aortic and mitral stenosis are extremely rare. Several mechanisms responsible for these valvular lesions have been reported: leaflet thickening, valvular perforation, and endocardial masses. Singh et al. [34] described a case of a 47-year-old male with aortic involvement in the course of GPA. The patient presented with mild aortic stenosis and moderate regurgitation due to aortic valve mass, which responded to immunosuppression [34]. Lacoste et al. [35] presented a case of man with aortic regurgitation that had to be operated because four months of immunosuppressive

therapy was not effective. Although aortic valve involvement appears to be more frequent, a mass lesion of the mitral valve has also been described in GPA. Dupuy et al. [36] described a case of a patient with severe mitral insufficiency caused by anterior leaflet perforation due to GPA infiltrates that required surgical mitral valve replacement. On the other hand, Attaran et al. [37] presented a case of a patient with extensive mitral mass extending to the aortic valve resulting in mild mitral stenosis as well as moderate regurgitation. In this case the lesion increased in size despite immunosuppressant and steroid treatment, and finally the patient underwent mitral valve replacement with a mechanical prosthesis implantation [37]. Espitia et al. [38] reported the case of a 60-year-old woman with severe inflammatory aortic and mitral valvular involvement with histopathological valvular lesions typical for GPA, which at presentation misleadingly suggest infectious endocarditis.

Myocarditis is a rare condition due to GPA. Weidhase et al. [39] presented a case of a 28-year-old male suffering from Wegener's granulomatosis, who died suddenly with signs of cardiac failure. Autopsy revealed diffuse granulomatous and necrotising giant cell myocarditis [39]. There are few cases of patients with GPA and constrictive pericarditis. It was described in patient with GPA who presented with progressive exertional dyspnoea and orthopnoea. The diagnosis was confirmed with cardiac catheterisation and the patient was referred for pericardial stripping [40].

Literature concerning cardiac involvement and immunosuppressive therapy is limited and controversial. In some cases prompt treatment with cyclophosphamide in the acute phase of the disease is very successful and provides resolution of cardiac complications [41]. However, there is also a case of a patient who died due to silent MI even after improvement of pulmonary and renal function [28]. Shanahan et al. [42] described a patient treated with cyclophosphamide, who developed cardiomyopathy with reduced left ventricular ejection fraction (LVEF) to 40%. Usually, it is very difficult to distinguish what was the preliminary cause of heart failure, because cardiomyopathy may develop in the course of the disease itself or as a complication of treatment. Cyclophosphamide is a well-known cause of cardiotoxicity and myocardial necrosis [43]. There is at least one case report of cardiomyopathy following IV cyclophosphamide therapy in a patient with GPA [44], as well as a case of a patient with intrinsic heart muscle involvement leading to cardiac failure [45].

Granulomatosis with polyangiitis must be included in the differential diagnosis when soft tissue thickening involves the coronary arteries and pericardium, even when no pulmonary or airway findings are identified [46]. Cardiac involvement occurred often in patients with a severe onset of the disease and careful monitoring is critical in this clinical setting. Therefore, risk stratification using cardiac imaging is recommended in all GPA patients, irrespective of symptoms or electrocardiography (ECG) abnormalities [17, 18].

## CARDIAC MANIFESTATION IN MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis shows a lower prevalence than GPA, it affects more men than women and starts at the age of 50 years. Renal involvement is the most common manifestation (79% patients) in MPA patients. However, MPA may also involve the nervous system, the skin, the musculoskeletal system, and gastrointestinal system [47, 48]. Cardiac involvement is uncommon and usually occurs in the context of multi-system involvement. In a series of 85 MPA patients only 10% had pericarditis, cardiac failure occurred in 18%, and MI in 2% [48]. In another Chinese cohort cardiac involvement was present in one-fifth of the patients, with pericardial involvement (pericarditis and pericardial effusion), cardiomyopathy, aortic incompetence, and rhythm disturbances being described [49].

## CARDIAC MANIFESTATION IN EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Eosinophilic granulomatosis with polyangiitis is a rare form of systemic, necrotising small-vessel vasculitis. EGPA is characterised by bronchial asthma, eosinophilia, and eosinophilic tissue infiltration of various organs with granuloma formation [5, 50]. It is a rare disease with the annual incidence of 2.4–6.8 cases/million inhabitants, and a prevalence of 11–14 cases/million in the general population [50]. Its frequency is highest at the age of 40–60 years with equal gender and ethnic distribution. The pathogenesis of the disease is still unclear; however, it is often assumed to be an autoimmune disease due to altered immune response and the presence of ANCA in about 40% of patients [51]. In a study by Sinico and Bottero [52], ANCA-positive patients were more likely to have disease manifestation due to small-vessel vasculitis, including necrotising glomerulonephritis, mononeuritis, and purpura, whereas ANCA-negative cases were more likely to have cardiac and lung involvement. EGPA is a systemic disease and may affect almost any organ. Most of the patients complain of general symptoms, such as malaise, fatigue, fever, arthralgia, and weight loss. The respiratory tract involvement consists of asthma and is present in almost all patients. Neurological involvement is also typical for EGPA, and can be found in up to 76% of patients [53]. Of the three types of AAV, cardiac involvement is the most common in EGPA, seen in approximately 16–92% of patients. Cardiac involvement, whether manifesting subclinically or clinically, is a poor prognostic factor. Two main mechanisms are postulated in the development of cardiac involvement in EGPA patients: vasculitis-related ischaemia and eosinophilic infiltration of the myocardium. Any cardiac structure can be involved, and patients present with myocarditis with cardiomyopathy and heart failure, pericarditis with pericardial effusion (up to 25% of patient), ventricular and supraventricular arrhythmias, coronary arteritis, valvulopathy, intracavitary cardiac thrombosis, and sudden cardiac death [53]. There are some

cases in literature describing dilated cardiomyopathy in patients with EGPA [54, 55]. Jeong et al. [56] presented a case of reversible dilated cardiomyopathy and intracardiac thrombi, which was diagnosed by MRI in an EGPA patient presenting with multifocal cerebral infarction [56]. Ischaemia and MI in EGPA patients are combined with the inflammatory process and eosinophil accumulation, with epicardial coronary arteries rarely demonstrating any changes during the coronary angiography [57]. Cardiovascular involvement is usually an early manifestation, but it can also occur later in the course of the disease. The majority of patients with heart involvement are asymptomatic. Subclinical cardiac involvement has been described using multimodality screening with ECG, transthoracic echocardiography, and MRI in up to 90% of patients with EGPA in clinical remission [53]. Moreover, Szczeklik and Miszański-Jamka [53] showed in their study that a greater degree of peripheral blood eosinophilia at baseline was correlated with higher prevalence of rhythm disturbances and lower LVEF. Therefore, all patients with EGPA should be studied not only with a detailed history of cardiac symptoms and ECG, but also with echocardiography. In patients with any abnormalities in echocardiography cardiac magnetic resonance should be performed. Cardiac involvement carries a poor prognosis. It causes 50% of the deaths of EGPA patients and is the first cause of death of these patients. Therapy with high-dose corticosteroids plus immunosuppressive agents, particularly cyclophosphamide in case of myocardial inflammation, is a life-saving procedure [58]. The use of immunosuppressives to control the activity of EGPA in addition to conventional heart failure medical therapy should be considered in patients with depressed left ventricle systolic function due to myocarditis [56].

### CARDIOVASCULAR MULTIMODALITY IMAGING

Cardiac involvement in AAV patients can be diagnosed using ECG, echocardiography, 24-h ECG Holter monitoring, nuclear techniques, multislice CT, endomyocardial biopsy, and MRI.

Echocardiography remains the routine cornerstone of cardiovascular evaluation. Transthoracic echocardiography may detect cardiac chamber enlargement, systolic and diastolic left ventricular dysfunction, valve dysfunction, pericarditis, and cardiac thrombus. Echocardiography may be useful to differentiate between cardiac involvement in EGPA and coronary artery disease, in which regional systolic dysfunction corresponds with epicardial coronary artery supply [53]. The two-dimensional speckle tracking strain, strain rate, and rotation analysis may be used for detailed assessment of myocardial systolic and diastolic dysfunction. Interestingly, systolic left ventricular dysfunction in EGPA predominately correlates with decline in global longitudinal and circumferential, but not radial, myocardial deformational parameters, indicating the presence of impaired contraction of inner and middle myocardial layers with preserved function of outer myocardial

fibre layer [59]. However, a normal echocardiogram does not always exclude cardiac involvement and identify heart disease.

Recent studies have demonstrated that cardiac MRI might be the most sensitive method for early detection and serial follow-up of cardiac involvement in EGPA patients [60, 61]. MRI can demonstrate not only the involvement of whole myocardium of all cardiac chambers, but also pericardial involvement. MRI offers reliable and reproducible information about myocardial function, inflammation, perfusion, and fibrosis. It is a “gold standard” in right ventricle assessment. MRI also helps in differential diagnosis between various types of scar (due to coronary artery disease or due to inflammation or vasculitis) [22]. Therefore, MRI is a necessary adjunct complementary to echocardiography, especially in new onset heart failure and when there are conflicting data from clinical, electrocardiographic, and echocardiographic evaluations. According to a new study fluoro-2-deoxyglucose positron-emission tomography (FDG-PET) together with MRI study might help to distinguish between local fibrosis or active inflammation in EGPA patients [62].

Multislice CT plays a diagnostic role not only in identifying the extent of calcification in coronary arteries but also in detecting significant artery stenosis and tissue characterisation of the atherosclerotic plaque. CT scan is the technique of choice for assessment of pulmonary embolism and pulmonary hypertension secondary to recurrent pulmonary emboli [63].

Multimodality imaging in AAV helps to detect subclinical cardiac involvement, which may have an impact on patient prognosis. In a cohort of 91 Dutch patients with GPA and EGPA cardiac involvement shown by multimodality screening (ECG, echocardiography, MRI, coronary angiography, and endomyocardial biopsy) was associated with significantly increased mortality compared to those without cardiac involvement [18].

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