Kardiologia Polska 2018; 76, 1: 77–82; DOI: 10.5603/KP.a2017.0187 ISSN 0022–9032

ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Atherosclerosis in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis

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INTRODUCTION

The primary systemic vasculitides are heterogeneous, multisystem disorders characterised by inflammation and necrosis of small and medium blood vessels. Their aetiology is unknown. The most common subgroup often associated with antineutrophil cytoplasmic autoantibodies (ANCA) is ANCA-associated vasculitis (AAV). Three types of AAV have been identified: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (Churg Strauss/EGPA), and microscopic polyangiitis (MPA) [1].

The AAVs as a group have an annual incidence of 20 per million, with GPA accounting for about half in northern European populations, MPA a third, and the rest EGPA. Early in the 20th century AAV resulted in death within weeks to months. The introduction of immunosuppression with alkylating agents and glucocorticoids as standard therapy, but also widespread availability of renal replacement therapy, have significantly reduced mortality in patients with AAV. Nowadays, ANCA-associated vasculitides is a chronic disease characterised by periods of remission and relapse. With prolonged survival, patients may experience long-term sequelae as a result of their vasculitis or its treatment [2].

In the early phases of the AAV, the symptoms can be non-specific and a high index of suspicion is required to achieve an early diagnosis. Symptoms that should prompt consideration of a diagnosis of vasculitis are unexplained systemic disturbance, arthritis or arthralgia, cutaneous lesions, polymyalgia, episcleritis, neuropathy, microscopic haematuria, proteinuria, pulmonary infiltrates or nodules, and maturity-onset asthma and persistent upper airways symptoms. Acute phase proteins such as C-reactive protein (CRP) and erytrocyte sedimentation rate are typically elevated in the acute phases of most vasculitides. It is important to recognise that a negative ANCA does not exclude vasculitis and a positive ANCA does not necessarily prove disease [3]. ANCA specificity is important, with the presence of PR3 ANCA

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Received: 21.07.2017 **Accepted:** 05.09.2017 **Available as AoP:** 29.09.2017

being strongly suggestive of a diagnosis of GPA, especially in Caucasian populations. Myeloperoxidase (MPO) ANCA is less specific, but is most frequently associated with MPA and EGPA. One third of cases with EGPA or localised GPA may be ANCA negative [4].

Eosinophilic granulomatosis with polyangiitis (Churg Strauss/EGPA)

The major clinical manifestations of EGPA are asthma, hypereosinophilia, and extrapulmonary manifestations of systemic vasculitis. In ANCA-positive patients the vasculitic pattern of the disease is dominant with more common renal involvement, neuropathy, and skin pathology compared to ANCA-negative patients. In the latter group, both lung and cardiac involvement are more frequent. Among the systemic vasculitides cardiac involvement is the most common in EGPA. The cardiac manifestations in EGPA are highly variable, ranging from myocarditis, pericarditis with pericardial effusion, heart failure, arrhythmia, and cardiac valve involvement, to coronary artery vasculitis [5]. The presence of cardiac involvement in EGPA patients deteriorates the prognosis and increase mortality. Nearly 50% of deaths in EGPA patients are related to cardiovascular disease (CVD) and occur most commonly within the first months after diagnosis [6]. According to the Five-Factor Score prognostic scale, cardiac involvement is an indication for adding further immunosuppression to the corticosteroid treatment [7].

Granulomatosis with polyangiitis (GPA)

In GPA, granulomatous inflammation of the respiratory tract, systemic vasculitis, and necrotising glomerulonephritis are found. Clinically, the disease is characterised by symptoms of the upper respiratory tract, such as bloody nasal discharge, nasal ulceration, chronic sinusitis, and otitis. Later on, manifestation of small-vessel vasculitis may occur in virtually every organ. According to literature the two most common cardiac manifestations are pericarditis and coronary arteritis (50% of cases), but endocarditis, myocarditis, and conduction system disturbances are also found in GPA patients [8].

Microscopic polyangiitis (MPA)

In MPA, most patients present with systemic symptoms, such as fever, malaise, arthralgia, myalgia, and skin vasculitis. Later on, a renal-pulmonary syndrome often occurs. Cardiac involvement is uncommon and usually accompanies involvement in other organs. In a cohort of MPA patients with cardiac involvement, the most common was: pericarditis with pericardial effusion, cardiomyopathy, aortic regurgitation, and rhythm disturbances [9].

CARDIOVASCULAR RISK IN VASCULITIS

There is an increased cardiovascular (CV) risk in patients with AAV. Within five years of diagnosis of GPA or MPA, 14% of patients will have a CV event [10]. In patients with vasculitis, PR3-ANCA is associated with a reduced CV risk compared with MPO-ANCA or negative ANCA status. Suppiah et al. [10] constructed and validated a tool to quantify the risk of a CV event based on age, diastolic hypertension, and PR3-ANCA status, in patients without prior CVD. Also in a retrospective review of the Danish National Hospital Register, patients with GPA showed an increased rate of early and late CV events within the first five years after a diagnosis of GPA, compared to the general population [11]. Early deaths in patients with AAV are due to the disease itself or complications of immunosuppressive drugs [12]. Several studies have now shown that, during long-term follow-up, CVD is a major cause of mortality in patients with ANCA-associated vasculitis [11, 13].

ATHEROSCLEROSIS IN AVV

Atherosclerosis is a chronic inflammatory disease of the arterial intima [14]. Vessel inflammation is thought to result from endothelium injury caused and sustained by many potential stimuli, such as oxidative stress derivates, heat-shock proteins, shear stress, or infections. Development of accelerated atherosclerosis, which leads to coronary artery disease, stroke, and other complications, is an important cause of morbidity and mortality in different systemic autoimmune diseases, including rheumatoid arthritis (RA), systemic sclerosis, systemic vasculitis, systemic lupus erythematosus (SLE), and primary antiphospholipid syndrome [15]. AAV is characterised by inflammation, and this is hypothesised to be the main factor that accelerates atherosclerosis in these patients. Systemic inflammation and immunological abnormalities result in accelerated atherosclerosis, independent of classic risk factors. Endothelial dysfunction, which is a recognised risk factor for CVD, has been shown to be present in ANCA-associated vasculitis and is independent of disease activity or renal involvement [16]. Raza et al. [17] assessed endothelial function by measuring flow-mediated brachial artery vasodilatation after reactive hyperaemia and found significantly impaired vasodilatation in AVV patients. Normalisation of endothelial function after the treatment of AVV suggests that early suppression of disease activity in chronic inflammatory disorders may reduce long-term vascular damage [17]. Arterial stiffness is another important and early determinant of the atherosclerotic process [18]. By measuring pulse waveforms and pulse wave velocities, Booth et al. [19] demonstrated that the aorta and systemic arteries were quantitatively more rigid in patients with active ANCA-associated vasculitides than those in remission or controls. Furthermore, arterial stiffness was positively correlated with the CRP level, but not with ANCA status, disease duration, prednisone dose, or serum tumour necrosis factor-alpha (TNF-α) level.

Patients with AAV often have impaired renal function as a result of their disease, although impaired renal function also increases CV risk. A retrospective study by Morgan et al. [20] found that AAV patients had more than double the risk of a CV event compared with the chronic kidney disease control

group. Analysis showed that both traditional and disease-related factors contributed to higher incidence of CV events in the AAV group, with previous CVD, dialysis dependence, and smoking being the strongest predictors of events. Dyslipidaemia is a recognised risk factor for atherosclerosis development. In patients with systemic vasculitis, high-density lipoprotein cholesterol (HDL-C) levels are decreased, whereas low-density lipoprotein cholesterol (LDL-C) levels are not elevated, but elevated LDL-C levels occur when moderate to severe proteinuria is present [21]. The prevalence of metabolic syndrome is significantly increased in AAV. In Petermann Smits et al.'s [21] study, 43% of 91 AAV patients met the 2005 National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP-III) definition of metabolic syndrome compared with just 25% of age- and gender-comparable healthy controls, regardless of current or accumulated prednisone use. Metabolic syndrome is associated with a more pro-inflammatory state in AAV and might increase the risk of developing a relapse of AAV [21]. Increased intima-media thickness (IMT), assessed by carotid ultrasound, is associated with the prevalence of CVD and accelerated development of atherosclerosis. Carotid ultrasound with measurement of IMT is a well-established tool for atherosclerosis imaging and CV event prediction [22]. In a study by de Leeuw et al. [23] IMT was found to be increased in GPA patients in the inactive phase of the disease, compared to healthy controls. This difference could not be explained by traditional risk factors, suggesting that the disease itself contributes to the development of atherosclerosis [23]. In another study by Chironi et al. [24] it was found that subclinical atherosclerosis demonstrated by plaques in carotid and femoral arteries and abdominal aorta is more frequent in AVV patients than in the control group. Atherosclerosis is considered to be a chronic inflammatory disorder. CRP is a marker of systemic inflammation and is described as an independent prognostic marker of CVD. Several studies have suggested that CRP may contribute directly to the development of atherosclerosis because it induces the expression of adhesion molecules on the endothelial surface and promotes the adherence of leucocytes [25]. Thus, CRP could be a direct link between autoimmune disease, characterised by systemic inflammation, and an increased risk for CVD. But the question remains as to whether this is a reflection of the greater prevalence of atherosclerotic changes in the vessel wall or of activity of vasculitis. Systemic vasculitis is defined as systemic and vessel-wall inflammation. However, precise characteristics of vessel-wall inflammation in atherosclerosis differ slightly from those of vasculitis. TNF-α and interferon-γ-producing T-helper (Th)1 lymphocytes are among the predominant cell population infiltrating into atheromatous plaques, along with macrophages and Th1 cells [26]. TNF-α is also strongly implicated in the pathogenesis of vasculitis, especially ANCA-associated vasculitides, but Th1 lymphocytes are far less prominent within the vessel-wall lesions of small-vessel vasculitides, with the exception of GPA lesions [27]. Matrix metalloproteinases (MMP) and their endogenous tissue inhibitors (TIMPs) have been found to be elevated in atherosclerotic lesions and in the serum of individuals with CVD. They are intricately involved in normal matrix turnover and can be produced by activated monocytes, smooth muscle cells, mastocytes, basophils, and some lymphocytes. High plasma levels of MMP2, MMP3, and TIMP1 were detected in a study on 15 GPA patients, who also had elevated MMP8 values when vasculitis was active, with TIMP1 and MMP8 being significantly associated with CRP levels [28]. In another study carried out on 29 patients with inactive GPA, hs-CRP, MMP3, MMP9, and TIMP1 levels were also elevated [29]. The multifaceted pathophysiology of premature atherosclerosis in small-sized vessel systemic vasculitides is presented in Table 1.

Table 1. Potential mechanisms of accelerated atherosclerosis in ANCA-associated vasculitis

Direct effects
Endothelial dysfunction:
Antibody-mediated endothelial cell damage
Immune complex-mediated endothelial cell damage
Cytokine-mediated endothelial cell damage
Arterial stiffness
Prothrombotic milieu
Dysfunctional high-density lipoprotein
Immune mechanisms:
Cytokines (TNF-α, IL-6)
Adhesion molecules
Ox-LDL/anti-ox-LDL
Anti-HSP
MMS/TIMPS
AECAs
ANCAs
Indirect effects
Hypertension
Diabetes
Renal dysfunction
Increased body mass index
Dyslipidaemia

CORONARY ARTERY DISEASE IN AVV

Coronary artery vasculitis leading to myocardial infarction is rare and mostly restricted to case reports [30, 31]. Gatenby et al. [32] described a 28-year-old man who presented with a picture of classical GPA, and who, in the absence of fulminating renal or respiratory disease, died from myocardial infarction. In another case of a patient presenting with a symptomatic myocardial infarction as the initial presenting

symptom of GPA, the coronary angiogram showed that the patient had developed coronary vasculitis, whilst having only mild upper respiratory tract symptoms and few of the constitutional symptoms typical of generalised GPA [33]. Ward et al. [34] showed a case of a 72-year-old woman who presented with acute coronary syndrome. There was diffuse coronary ectasia and severe stenosis in the proximal left anterior descending artery consistent with coronary vasculitis. Despite treatment with high-dose immunosuppression, she underwent percutaneous coronary intervention for refractory angina [34]. In a study by Dennert et al. [35], 13 out of 32 enrolled patients with EGPA complained of chest pain and dyspnoea and had coronary angiography performed. Two patients showed a lesion (> 70% stenosis) in the left anterior descending coronary artery, three had wall irregularities, and eight patients had no abnormalities in coronary arteries [35]. In a recent study by Aviña-Zubieta et al. [36] patients with GPA had a significantly increased risk of myocardial infarction and a non-statistically significant trend toward an increased risk of ischaemic stroke. Although coronary angiography remains the gold standard for diagnosing coronary stenosis, non-invasive and more reliable methods, such as magnetic resonance imaging (MRI) and positron emission tomography scan, have been proposed in order to detect subclinical microcirculation abnormalities. Contrast enhancement in MRI implies acute myocardial damage or chronic fibrosis. This kind of change may be seen in all kinds of cardiac disease, such as myocardial infarction, myocarditis, myocardial infiltrative disease, and hypertrophic cardiomyopathies. Subendocardial late gadolinium enchancement (LGE) is characteristic of ischaemic heart disease, and therefore coronary artery disease should be ruled out when it is observed. With this method, ischaemic and non-ischaemic cardiomyopathies can be distinguished by experienced radiologists [37, 38]. In a series of 11 EGPA patients undergoing MRI, various forms of myocardial injury were detected in all patients. Mean left ventricular ejection fraction was 45% with impairment of left ventricular function in six patients, oedema in four, pericardial effusion in seven, and LGE-positivity in nine, including some with normal left ventricle size and ejection fraction [39].

INFLUENCE OF MEDICAL TREATMENT OF AVV ON ATHEROSCLEROSIS DEVELOPMENT

Glucocorticoids are an important component of induction therapy in systemic vasculitis. However, AVV patients are likely to be on low-dose corticosteroid therapy for a number of CV risks and development of atherosclerosis, by accelerating the development of diabetes mellitus, dyslipidaemia, and hypertension. Patients on current glucocorticoid therapy have a two- to three-fold greater risk of developing heart failure and a one- to two-fold greater risk of developing ischaemic heart disease [40]. Total cholesterol, LDL-C, and HDL-C all increase during corticosteroid therapy. However, corticosteroids may also have a protective role in vasculitis by reducing systemic inflammation and improving endothelial dysfunction [40, 41]. Other medicines that are used in patients with AAV such as: cyclophosphamide, azathioprine, and mycophenolate mofetil do not increase cholesterol levels. Cyclophosphamide is a synthetic myelosuppressive drug that decreases inflammation-associated cells and increases circulating progenitor cells. In an experimental study, it was demonstrated that oral treatment with cyclophosphamide inhibits atherosclerosis initiation and progression in an ApoE–/– mouse model [42]. Methotrexate is commonly used as a maintenance therapy in AAV. The primary anti-inflammatory actions of methotrexate are attributable to adenosine release. Adenosine, a nucleoside produced by many cells and tissues in response to physical or metabolic stresses, is an endogenous anti-inflammatory mediator. Systematic reviews and meta-analyses have shown a decreased risk of CV risk in patients receiving methotrexate [43]. Methotrexate also enhances cholesterol uptake into HDL thereby promoting reverse cholesterol transport and contributing to decreased atherogenesis [44]. In an animal model of atherosclerosis (New Zealand rabbits on a diet with 1% cholesterol), use of a methotrexate nanoemulsion that concentrated the drug at sites of atherogenesis resulted in deceased atherosclerotic plaques and improved IMT, with reduction in proinflammatory cytokines and an increase in interleukin 10 in these plaques [45]. In a study by Moreira et al. [46] performed in acute myocardial infarction patients, there was a reduction in myocardial necrosis biomarkers (CK, CK-MB and troponin) in the levels of B-type natriuretic peptide, hs-CRP, and an improvement of left ventricular ejection fraction and TIMI frame count in the methotrexate group compared to the placebo group [46]. Azathioprine is used as a maintenance agent in AAV patients. There is evidence for atherosclerosis inhibition with azathioprine in an animal model by decreasing the levels of monocyte chemoattractant protein 1 and reducing monocyte adhesion [47]. Use of another maintenance drug, mycophenolate mofetil, has been associated with decreased CV risk in patients undergoing kidney transplantation [48]. Rituximab is now considered as first-line therapy for the management of AAV patients. In a study by Kerekes et al. [49] rituximab has shown favourable alterations in lipid profile, with decreased triglycerides and increased HDL, but also early and sustained favourable effects on endothelial dysfunction and decreased common carotid IMT.

CONCLUSIONS

Patients with antineutrophil cytoplasmic autoantibody-associated vasculitis have increased mortality rate as a consequence of CVD. Experts recommend that the evaluation for cardiac involvement in patients with AAV should include not only a detailed history of cardiac symptoms and electrocardiography, but also imaging with echocardiography or cardiac MRI. Since

AVV patients with cardiac involvement has been associated with a worse prognosis, early diagnosis is advocated because appropriate therapy may prevent progression of cardiac disease. Measures to reduce the risk of CVD should be integral to the management of systemic vasculitis. The preventive therapy for accelerated atherosclerosis in systemic vasculitis should be based on an aggressive approach against inflammation and against risk factors of premature atherosclerosis, such as hypertension, smoking, inactivity, obesity, and unhealthy diet. Aggressive therapy with antihypertensive, lipid-lowering, and renoprotective agents should be implemented in cases of hypertension, dyslipidaemia, and impaired renal function. Symptoms suggestive of myocardial ischaemia must lead to an immediate and comprehensive cardiologic evaluation. All patients with antineutrophil cytoplasmic autoantibody-associated vasculitis should be subjected to prolonged follow-up at dedicated clinics and frequent screening for CV risk factors.

Conflict of interest: *none declared*

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Cite this article as: Życińska K, Borowiec A. Atherosclerosis in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Kardiol Pol. 2018; 76(1): 77–82, doi: 10.5603/KP.a2017.0187.