

ANCA-Associated Vasculitides—An Update

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are characterized by destruction of small vessels, granulomatous inflammation of the respiratory tract and necrotizing glomerulonephritis. This review describes the clinical diagnosis and therapy as well as the pathophysiology of ANCA-associated vasculitides with a specific focus on the interplay of ANCAs with activated neutrophils and the deleterious pathophysiological consequences of neutrophil-endothelium interaction.

Keywords

Vasculitis, Anti-Neutrophil Cytoplasmic Antibodies, Neutrophils

1. Introduction

Vasculitides are defined by the presence of inflammatory leukocytes in vessel walls with reactive damage to mural structures. This leads to the loss of vessel wall integrity, compromise of the lumen with downstream tissue ischemia and necrosis. Vasculitis may occur as a primary auto-inflammatory process or may be secondary to another underlying disease such as inflammatory bowel disease, rheumatoid arthritis, neoplasia or viral infections [1] [2]. Classically, the vasculitides have been categorized by the sizes and types of blood vessels most commonly affected leading to a distinction between large-, medium sized- and small vessel vasculitis [3]. The presence or absence of anti-neutrophil cytoplasmic antibodies (ANCA) is an addition to proposed classification criteria [4]. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) comprise granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome). These diseases are characterized by Pauci-immune necrotizing small-vessel vasculitis and glomerulonephritis, combined with granulomatous inflammation, particularly in the airways, in GPA and EGPA [5]. The annual incidence of AAV as a group is 10 - 20/million/year with regional differences. In northern Europe including Germany GPA is more common whereas in Southern Europe MPA has a higher occurrence [6]. The peak incidence is at 65 to 74 years

of age, with a greater incidence in men, and the mortality ratio is 2.6 compared to the general population with most deaths related to infection due to the immunosuppressive therapy [7] [8].

2. Classification of Granulomatosis with Polyangiitis

In January 2011 the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League against Rheumatism recommended that the name Wegener’s granulomatosis be changed to granulomatosis with polyangiitis, abbreviated as GPA [9]. The hallmark of GPA is a necrotizing granulomatous inflammation of the upper and/or lower respiratory tract, systemic small-vessel necrotizing vasculitis and necrotizing glomerulonephritis in conjunction with the occurrence of ANCA directed to the neutrophils’ proteinase 3 (PR3).

3. ACR Criteria

The 1990 ACR criteria include:

- Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge);
- Abnormal chest radiograph showing nodules, fixed infiltrates or cavities;
- Abnormal urinary sediment (microhematuria or red cell cast);
- Granulomatous inflammation on biopsy of an artery or perivascular area.

It should be noted that these criteria have less value in separating MPA from GPA [10].

4. Chapel Hill Consensus Conference Criteria (CHCC)

According to the 1992 Chapel Hill Consensus Conference Criteria GPA, MPA and CSS are distinguished from other vasculitides by the absence of immune deposits. The potential value of ANCA serology was noted but not included as a criterion for diagnosis. GPA is characterized by [11]:

- Granulomatous inflammation involving the respiratory tract;
- Necrotizing vasculitis affecting small to medium-sized vessels;
- Necrotizing glomerulonephritis is common.

5. Clinical Presentation, Diagnosis and Therapy

Reliable and validated diagnostic criteria for ANCA-associated vasculitides are still not available, although a large prospective international study aimed at establishing these criteria (Diagnosis and Classification of Vasculitis Study [DCVAS]) is underway. [12] Patients often present with prodromal symptoms such as fever, migratory arthralgias, malaise, anorexia and weight loss. These might last for weeks or months without the evidence of specific organ involvement listed in **Table 1** [13]-[19].

The clinical presentation may be a first hint towards the diagnosis of GPA. Routine laboratory tests should be performed. Common abnormalities include leukocytosis, thrombocytosis, an elevation in the erythrocyte sedimentation rate and C-reactive protein levels and normochromic, normocytic anemia [16]. Approximately 90% of patients with active, generalized GPA are ANCA-positive. In limited forms of the disease ANCA may only be

Table 1. Organ manifestation of Granulomatosis with polyangiitis.

Organ	Manifestation
Ear, nose throat	Nasal crusting, sinusitis, otitis media, persistent rhinorrhea, purulent/bloody nasal discharge, oral/nasal ulcers, bony and cartilage destruction (e.g. saddle nose deformity)
Lung	Cough, dyspnea, stridor, hemoptysis, pleuritic pain, tracheal or subglottic stenosis, pulmonary fibrosis, pulmonary arterial hypertension, parenchymal lung nodules
Kidney	Acute renal failure, pauci-immune crescentic necrotizing glomerulonephritis, interstitial nephritis
Skin	Leukocytoclastic angiitis, purpura, ulceration, urticaria, livida reticularis, nodules
Eye	Conjunctivitis, corneal ulceration, episcleritis/scleritis, optic neuropathy, retinal vasculitis, uveitis, diplopia, proptosis
Nervous system	Mononeuritis multiplex, cranial nerve abnormalities, central nervous system lesions

found in 60%. Thus a positive ANCA test strongly suggests the diagnosis of vasculitis but the absence of ANCA does not exclude the diagnosis of GPA [20]. Serum-creatinine, a calculated estimated filtration rate and a urine analysis help to determine the presence of kidney injury. A chest x-ray and CT disclose pulmonary lesions.

The diagnosis should be confirmed by a tissue biopsy at a site of active disease. Biopsies are most commonly obtained from the kidney or skin and less commonly from the nose or the lung. Therapy of GPA has two components: The induction of remission and maintenance immunosuppressive therapy to prevent relapse. The standard of care for patients with organ-threatening disease is cyclophosphamide in combination with glucocorticoids, although two randomized studies have shown that rituximab was as effective as cyclophosphamide in inducing remission of patients with newly diagnoses or relapsing GPA [21] [22]. Maintenance therapy includes methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and in refractory cases also IVIg, infliximab and anti-thymocyte globulin [23].

6. Pathophysiology of GPA

Both innate and adaptive immune mechanisms are involved in the pathogenesis of GPA. There are several hints that the antigen-driven immune response is initiated in the upper respiratory tract with involvement of endonasal B cells [24] [25].

In a first step macrophages are stimulated by microbial products in a Toll-like receptor way to release proinflammatory cytokines [5]. Tadema *et al.* demonstrated increased expression of Toll-like receptors by monocytes and natural killer cells of patients with GPA. [26] Cytokines then prime and activate neutrophils to release Proteinase-3 and endothelial cells to express adhesion molecules, thus recruiting inflammatory cells like monocytes and macrophages. These cells, in response to TLR ligands, secrete more proinflammatory cytokines, including interleukin 23, driving T-cells towards a T helper cell 17 phenotype. Secreted IL-17 then attracts neutrophils and stimulates granuloma formation. Neutrophils adhere to the endothelium and release the auto-antigen PR3. IL-21 derived from follicular T helper cells and B-cell activating factor (BAFF) released from activated neutrophils activate B-cells to produce PR3-ANCA. PR3-ANCA then fully activate primed neutrophils resulting in degranulation and the production and release of reactive oxygen species leading to leukocytoclastic vasculitis. PR3-ANCA formation is perpetuated by the lack of function of regulatory T cells (Treg) and regulatory B cells (Breg) [5]. Treg cell frequency is increased in patients with active disease, but the Treg cells have a decreased suppressive function. These patients also carry CD4+ T cell populations that are resistant to Treg cell suppression and produce inflammatory cytokines [27]. In GPA an expansion of CD4 T cells occurs in the CD4+ effector memory population. The generation of CD4 TEM cells requires a strong and persistent trigger, suggesting that, also during remission, T cells in GPA are in a persistent state of ongoing immunological trigger [28]. At the functional level CD4+ TEM cells mimic NK cells by their cytotoxicity and surface expression of NKG2D [29]. One of the NKG2D ligands is the major histocompatibility complex class I chain-related molecule A (MICA), which is absent on normal cells, but expressed upon cellular injury and stress [30].

The formation of granulomatous lesions differs from T cell mediated granulomatous inflammation known from tuberculosis or sarcoidosis. Here the initial step is the formation of a micro-abscess by neutrophils due to neutrophil activation by ANCA and accumulation in the extravascular tissue. This tissue injury leads to an immune response attracting monocytes. They transform into macrophages, which in turn recruit T-cells [31]. It has been speculated that local antigen presentation is maintained by such macrophages [32]. Consistent with these findings, a purulent neutrophil reaction with the formation of micro-abscesses is present in respiratory tract lesions of initial GPA [33]. Furthermore, granulomatous lesions in GPA contain clusters of PR3 surrounded by antigen-presenting cells, Th1-type CD4+CD28- T cells, maturing B and plasma cells suggestive of a neoformation of lymphoid like structures in GPA [34].

7. Characteristics of ANCAs

It was in 1985, when the presence of antineutrophil cytoplasmic antibodies (ANCA) was linked to Granulomatosis with Polyangiitis for the first time [35]. Within several years, a relationship among ANCA, GPA, microscopic polyangiitis (MPA), and “renal-limited” vasculitis (pauci-immune glomerulonephritis without evidence of extra-renal disease) had been established [36] [37]. When incubated with ethanol-fixed human neutrophils, two major ANCA immunofluorescence patterns are observed. With the C-ANCA pattern, the staining is diffuse throughout the cytoplasm. In most cases, antibodies directed against PR3 cause this pattern [38], but MPO-

ANCA can occasionally be responsible. The perinuclear or P-ANCA pattern results from a staining pattern around the nucleus, which represents an artefact of ethanol fixation. Among vasculitis patients, the antibody responsible for this pattern is usually directed against MPO (and only occasionally PR3) [36]. Indirect immunofluorescence has a high sensitivity whereas enzyme-linked immunoassays have a higher specificity. Specific ELISAs for antibodies to PR3 and MPO are commercially available, and should be part of any standardized approach to the testing for ANCA [39].

PR3, also called myeloperoxidase, is specifically expressed by neutrophils and monocytes and belongs to the neutrophil serine protease family. It is classically localized in azurophilic granules with its homologs: elastase, cathepsin G and azurocidin. After phagocytosis of pathogens, PR3 is secreted in the phagolysosome to exert its microbicidal function [40]. Upon priming neutrophils express PR3 on their surface, usually in co-expression with CD177 although CD177 independent ways of expression have been described [41] [42].

The question whether ANCA themselves play a pathogenic role in the development of vasculitis has been discussed extensively. Mice injected with anti-MPO developed focal necrotizing crescentic glomerulonephritis [43] [44]. Chimeric mice with a human immune system also exhibited clinical and histological signs of systemic vasculitis affecting the kidneys and lungs after injection of anti PR3 containing IgG [45]. Transfusion of anti MPO containing blood via the cord can induce pulmonary hemorrhage and kidney involvement in a neonate [46]. Epigenetic changes associated with gene silencing of the ANCA auto-antigen-encoding genes and inappropriate expression of PR3 and MPO in ANCA vasculitis indirectly support a pathogenic role for ANCA [47]. Also an increase in ANCA titers can be a predictor of relapse and the successful treatment of with the B-cell depleting agent Rituximab supports a pathogenic role for ANCA [48] [49]. As described in more detail below ANCA can induce the respiratory burst of primed and unprimed neutrophils [42] [50]-[52]. However even in healthy individuals natural autoantibodies against MPO and PR3 can be detected, although in much lower titers than those of MPO/PR3 ANCA from patients with vasculitis. It is speculated that these natural autoantibodies are kept under control by anti-idiotypic antibodies [53]. In addition, nearly half of the patients with localized disease are ANCA negative and not in all cases conventional serological assays correlate with disease activity although this might be due to differences in ANCA epitope specificity [54] [55].

8. Interaction of ANCA and Polymorphonuclear Leukocytes (PMN)—The Role of Apoptotic PMN

Polymorphonuclear cells (PMN) are professional phagocytic cells of the innate immune system that act as the first line of defence against invading pathogens. PMNs, especially neutrophils, play a pivotal role in the acute injury of ANCA associated vasculitis since they are both effector cells responsible for endothelial damage and targets of autoimmunity [40]. Although some authors suggest that unprimed neutrophils express the ANCA antigen Proteinase-3 and neutrophilic respiratory burst can be stimulated by binding of ANCA, it is generally accepted, that an initial priming step is required for their pathophysiological function in AAV [40] [50]. Priming can be induced by inflammatory cytokines, adhesion, bacterial products (lipopolysaccharide), or lipid mediators. In their primed state, exposure to a second stimulus results in faster and stronger responses of the PMN [40]. In AAV, priming induces membrane expression of PR3 and MPO and subsequent binding of ANCA triggering PMN activation [42]. Primed neutrophils incubated with IgG purified from sera containing anti-PR3 ANCA or anti-MPO ANCA are able to produce superoxide anion and release lytic granular proteins *in vitro* [42] [51] [52]. ANCA-induced neutrophil activation requires both, antigen binding via Fc receptors (Fc γ RIIa or Fc γ RIIIb) as well as β 2-integrin engagement [40] [56]. The size and subset of PMN that display PR3 on their surface seems to be a stable feature of an individual, most likely genetically controlled. Witko-Sarsat *et al.* defines three types of phenotypes with low, intermediate and high expression of membrane-located PR3 (mPR3). The mPR3 high phenotype occurs significantly more often in patients with ANCA vasculitis [57] [58]. PMN from AAV patients also re-express genes coding for PR3, despite the fact that these genes are normally restricted to the promyelocytic stage during granulocytic differentiation [59].

PMN are not simple terminal effector cells but also show immuno-modulating features. By secreting a great variety of cytokines and chemokines they instruct all immune cells (monocytes, dendritic cells (DC), T cells and B cells) through an active cross-talk [40]. PMN traffic immature and mature DC to mucosal surfaces and lymphoid organs, produce chemoattractants for DC, modulate DC maturation and function and act as a transport vehicle for antigens to DC, thus playing an important role in the activation of T-cell responses controlled by DC

[60]. In addition PMN crosstalk with T-cells and exhibit a significant chemotactic effect toward Th1 and Th17 cell subsets by releasing CCL2, CXCL9, CXCL10, CCL20 and CCL2 [61]. Moreover, PMN are a major source of B-cell-Activating Factor (BAFF) and A Proliferating-Inducing Ligand (APRIL), which are both members of the TNF superfamily and implicated in fundamental processes of B lymphocytes homeostasis. Notably, serum levels of BAFF are elevated in GPA compared to controls [62]. In addition, ANCA primed PMN produce BLYS, a protein which promotes B-cell survival, and patients with ANCA vasculitis show increased serum levels of BLYS [63].

PMN from patients with AAV showed enhanced apoptosis compared to controls when activated by ANCA [64]. Apoptosis is a genetically programmed cell suicide, characterized by the condensation of cytoplasm and intracellular organelles, cleavage of nuclear chromatin, formation of apoptotic bodies with or without nuclear remnants and exposure of phosphatidylserine on the outer leaflet of the plasma membrane. All of these changes are related to the activation of caspases, an evolutionary conserved family of proteins that irreversibly commit a cell to die [65] [66]. The efficient clearance of apoptotic cells is crucial for tissue homeostasis. Otherwise, post-apoptotic necrosis leads to loss of membrane integrity and leakage of potentially cytotoxic and antigenic intracellular contents into the surrounding environment. Clearance is a process of engulfment and digestion of apoptotic cells by phagocytes and is mainly executed by tissue macrophages. Apoptotic cells display different so called eat-me signals on their surface, including externalized phosphatidylserine, oxidized LDL or Thrombospondin-1 binding sites as well as so called find-me signals like lysophosphatidylcholine to attract monocytes. The complex process of apoptotic cell clearance actively suppresses the initiation of inflammation and immune responses, in part through the release of anti inflammatory cytokines such as TGF- β , PGE2 or PAF through autocrine and paracrine mechanisms. In higher organisms non-ingested apoptotic cells might be a reservoir for autoantigens presented to the adaptive immune system and thus initiate and drive systemic autoimmunity. For example, mice lacking certain proteins involved in the bridging process between the apoptotic cell and the phagocyte develop auto-immune diseases resembling human lupus erythematosus [67]. ANCA-opsonized PMN develop the morphologic features of apoptosis without cell surface changes that normally accompany apoptosis, including phosphatidylserine expression. These ANCA primed PMN are less well cleared by phagocytic macrophages and eventually disintegrate, releasing cytotoxic contents [68] [69]. ANCA-opsonized PMN also show higher rates of apoptosis and increased ROS production, and their clearance by phagocytic cells triggers the production of proinflammatory cytokines. In addition, ANCA-opsonized apoptotic PMN translocate PR3 to their membrane leading to increased ANCA binding [51] [64] [70]-[74]. Immunization of rats with late apoptotic PMN leads to a break of tolerance against PMN and the production of ANCA [75] [76].

Another quite recently described pathway of neutrophil death is the formation of NETs (neutrophil extracellular traps). NETs are webs formed by chromatin and granule proteins that provide a high local concentration of antimicrobial molecules including PR3 [77]. ANCA binding to primed PMN induces the formation of NETs expressing the auto-antigen PR3. This may activate plasmacytoid dendritic cells, thus breaking the tolerance against self DNA and promoting auto immunity by production of interferon- α and the activation of auto-reactive B cells to the production of ANCA [78] [79].

9. Endothelium-Neutrophil Interactions in GPA

Endothelium-neutrophil interactions are essential to allow neutrophils to move toward inflammatory sites and to perform innate immune responses [80]. The transmigration of neutrophils through the endothelium includes a number of steps. The initial attachment of neutrophils to endothelial cells is termed rolling. Rolling is generally mediated by interactions between selectins on the endothelial cells and glycosylated ligands of the neutrophil and leads to a slowing down of the cells in the bloodstream. Endothelial selectins are upregulated in response to stimuli such TNF- α , interleukin-1 β (IL-1 β) or IL-17. These stimuli are generated during infection or inflammation and result in upregulation of P-selectin and E-selectin on the luminal surface of ECs. The neutrophil ligands, L-selectin and P-selectin ligand-1 (PSGL-1), are constitutively expressed on the tips of neutrophil microvilli. Selectin-mediated neutrophil-EC interaction only lasts seconds and is reversible. This step is followed by firm adhesion mediated by the β 2-integrins, LFA-1 (α L α 2), Mac-1 (α M β 2) and VLA-4 on neutrophils and their ligands on endothelial cells including ICAM-1, ICAM-2 and VCAM-1. Various chemokines have been found inducing integrin activation on neutrophils, such as platelet-activating factor (PAF), IL-8, fMLP, TNF- α , RANTES or bacterial products, like LPS. Two routes have been described for neutrophil migration through the endothelium: transcellular migration, whereby neutrophils penetrate the body of ECs, and paracellular migration

used by the majority of neutrophils, whereby they squeeze between two adjacent ECs. Paracellular migration of neutrophils is controlled by endothelial ICAM-1, ICAM-2, junctional adhesion molecule-A (JAM-A) and platelet endothelial cell adhesion molecule-1 (PECAM-1). Blocking or depletion of ICAM-1 or ICAM-2 revealed that they are both involved in guiding neutrophils to enter the EC-junctions. JAM-A is associated with further penetration of neutrophils, and finally PECAM-1 performs the last step of neutrophil transendothelial migration, which is demonstrated by the observation that in PECAM-1^{-/-} mice neutrophils are trapped between ECs and basement membrane [81] [82].

In AAV levels of circulating TNF- α and IL-8 are elevated creating an inflammatory environment that triggers β 2-integrin activation and adherence of circulating neutrophils to the endothelium [83] [84]. The rolling of ANCA-opsonized PMN is converted into firm adhesion even at minimal TNF- α concentration [85]-[87]. Indeed, increased glomerular endothelial ICAM-1 and VCAM-1 concentrations and increased levels of neutrophil β 2 and β 1-integrins are described in active AAV [88] [89]. Consistent with these findings, Cockwell *et al.* have located infiltrated PMN during acute vasculitis at or within the glomerular capillary loops with rather poor penetration into the interstitial tissue [90]. Adhesion leads to the expression of high levels of mPR3 that is accessible to plasma-derived ANCA [91]. Synergy of β 2-integrin outside signaling, TNF- α induced signaling and Fc γ R signaling of ANCA binding leads to an explosive oxidative burst and subsequent endothelial damage [92] [93]. Complement activation further amplifies the proinflammatory response of adherent PMN in the presence of ANCA. PMN-bound ANCA trigger the complement classic pathway exclusively on adherent PMN, a condition allowing access of ANCA to their antigens in plasma [80].

As described above, PR3 and CD177 are co-expressed on the membrane of a subset of PMN, and the proportion of mPR3⁺/CD177⁺ PMN is increased in patients with ANCA vasculitis. Anti-PR3 ANCA trigger degranulation and extracellular superoxide release from the CD177⁺ PMN subsets [94] [95]. Moreover mPR⁺/CD177⁺ PMN show a higher transendothelial migration probably due to CD177-triggered PECAM-1 signaling [94] [96].

Although PMN binding sites and the area of protein leakage are uncoupled, hence suggesting that the adhesion process is not the main inductor of vascular permeability, the close proximity of activated, ROS and proteases releasing PMNs to the endothelium may contribute to vascular permeability [97]-[101]. Moreover, interaction of PMN and endothelial cells in the phase of firm adhesion leads to cytoskeletal changes and disturbed integrity of the endothelial barrier. Altered barrier function facilitates diapedesis followed by endothelial apoptosis and detachment promoted by PMN-derived proteases and oxidants [80] [102]-[106]. One of the cellular markers for endothelial cell damage is the number of circulating endothelial cells which is significantly higher in patients with ANCA vasculitis and decreases with remission [107].

In conclusion, ANCA antibodies lower the threshold of neutrophil responses to inflammatory cytokines and result in a vigorous response in the vascular bed even before any diapedesis or migration [80].

10. What Triggers GPA and Its Relapse?

Staphylococcus aureus seems to play an important role in the stimulation of immune responses in patients with GPA. Carriers of nasal *S. aureus* express increased levels of intracellular TLR9, which are stimulated by bacterial CpG dinucleotide motifs. The latter, together with IL-2, have been reported to trigger autoreactive B-cells to the *in vitro* production of PR3-ANCA [26] [108]. Chronic nasal carriage of *S. aureus* is an independent risk factor for relapse [109]. Also, peptides from *S. aureus* can induce the production of antibodies to complementary PR3, which, in turn, could induce antibodies to PR3 via idiotypic-anti-idiotypic interactions [110]. However, an increase of antibodies to complementary PR3 could not be observed in all cohorts of patients with GPA [111]. It is speculated that *S. aureus* might directly prime neutrophils to translocate PR3 to the surface, thus increasing the susceptibility for PR-ANCA. Moreover, *S. aureus* may also activate B-Cells polyclonally by its cell-wall components, resulting in persistence of ANCA. Other known risk factors are the exposure to silica, which might evoke an immune response and inflammatory reactions via various pathways and accelerate the apoptosis of neutrophils [112]-[115]. Drugs, in particular propylthiouracil, hydralazine, anti TNF- α agents, sulfasalazine, D-penicillamine and minocycline, have also been described to be associated with an increased risk for developing GPA [116].

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