The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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ANCA-associated vasculitides

Julia U. Holle, Elena Csernok, Allan Wiik, Wolfgang L. Gross

1 Introduction

The ANCA-associated vasculitides (AAV) are comprised of Granulomatosis with Polyangiitis (formerly Wegener's Granulomatosis, GPA), Microscopic Polyangiitis (MPA) and Churg-Strauss Syndrome (CSS) (see [1] for review and Figs. 1 and 2). They share the features of small vessel vasculitis but are otherwise a heterogeneous group with different preferences of organ involvement and frequency of ANCA positivity. The AAV are classified according to the American College of Rheumatology (ACR) criteria and the Chapel Hill Consensus Conference (CHC) definitions (Table 1) [see 1 for review]. Due to efforts to eliminate eponyms in disease names, Wegener's granulomatosis was renamed in 2011 to Granulomatosis with Polyarteritis (GPA) [2].

In general, GPA and CSS are characterised by granulomatous lesions (especially of the respiratory tract) and small- to medium size vessel vasculitis in biopsy specimens, whereas MPA is a small to medium size vessel vasculitis without granuloma. Moreover, GPA is characterized by space-consuming lesions, e.g. orbital or pulmonary "granuloma" or masses. In CSS, asthma and eosinophilia in peripheral blood and affected tissues are also a hallmark of the disease. Generalised disease in GPA and CSS is usually preceded by a localised phase in GPA (upper and lower respiratory tract involvement, e.g. sinusitis) and a phase of refractory asthma/localized polypoid sinusitis and/or eosinophilia in CSS (Table 2). ENT manifestations/relapses of GPA may be associated with nasal carriage of *Staphylococcus aureus*. Vasculitis manifestations include alveolar haemorrhage, glomerulonephritis, sensorimotor polyneuropathy and represent potentially life-threatening organ manifestations. Virtually any organ can be affected by small vessel vasculitis (Table 2). ANCA are detected in almost all patients with MPA and GPA in the active generalised stage of the disease; in CSS, ANCA are present in only 40 % and their presence is associated with typical vasculitis manifestations such as glomerulonephritis. In GPA, ANCA are mainly directed against the neutrophil serine protease proteinase 3 (PR3), whereas, in MPA and CSS, ANCA mainly target the neutrophil enzyme myeloperoxidase (MPO). ANCA play a major pathogenetic

Table 1. Classification criteria of ANCA-associated vasculitides.

ANCA-associated vasculitis	American College of Rheumatology Criteria	Chapel Hill Consensus Conference Criteria
Granulomatosis with Polyangiitis (formerly Wegener's Granulomatosis)	**nasal or oral inflammation** **abnormal chest radiograph:** nodules fixed infiltrates or cavities **abnormal urinary sediment**: microhaematuria/ red cell casts **granulomatous inflammation on biopsy** *at least 2 of 4 criteria must be present*	granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-size vessels *necrotizing glomerulonephritis is common*
Microscopic Polyangiitis	no criteria	necrotizing vasculitis affecting small to medium-size vessels *necrotizing glomerulonephritis is very common, pulmonary capillaritis often occurs*
Churg-Strauss-Syndrome	**asthma** **blood eosinophilia** (> 10 % on white cell count) **mono- or polyneuropathy** **pulmonary infiltrates**, non-fixed **paranasal sinus abnormality** **extravascular eosinophils in biopsy** *at least 4 criteria must be present*	**eosinophil-rich and granulomatous inflammation of the respiratory tract**, **necrotizing vasculitis affecting small to medium-size vessels**, associated with asthma and blood eosinophilia

role in the induction of small vessel vasculitis, as they induce neutrophil activation in small vessels by interacting with their target antigens which are expressed on the surface of activated neutrophils [1].

The AAV are rare diseases: GPA is the most frequent AAV with an incidence of 9/Mill/yr. The incidence rates of CSS and MPA are 1–2.4/Mill/yr and 1/Mill/yr, respectively [3].

2 Diagnostic procedures for experts

AAV are multi-system disorders often affecting many organs. Therefore, they require a thorough patient inquiry regarding potential organ manifestations. The suspicion of AAV should be raised if a patient presents with refractory sinusitis or asthma, especially if these symptoms occur in the context of massive fever, weight loss, impaired kidney function (crescentic glomerulonephritis!), haemoptysis (alveolar haemorrhage), purpura (leukocytoclastic vasculitis of the skin), or sensorimotor paresis (polyneuropathy). Proptosis of the bulbus may be a sign of

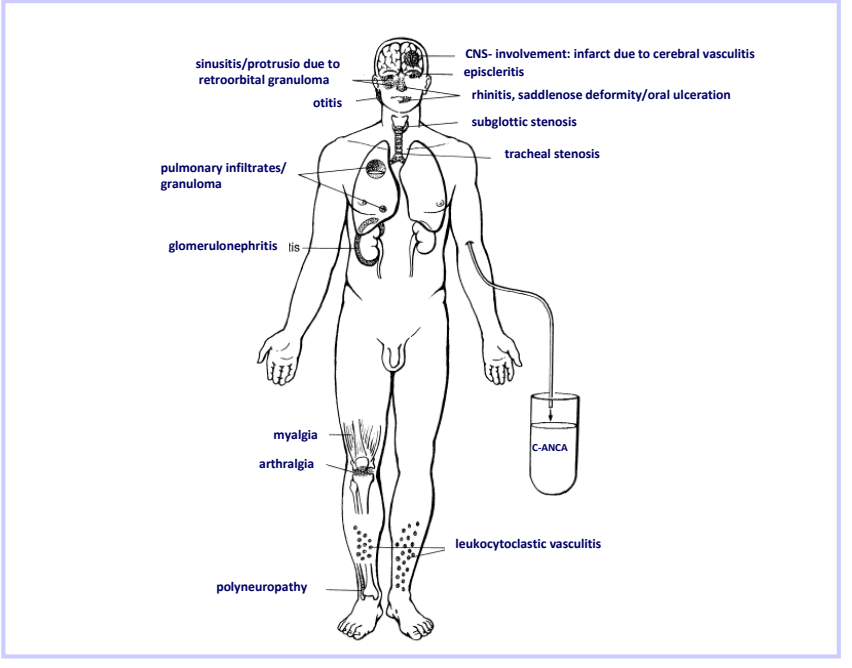

Figure 1. Clinical manifestations of Granulomatosis with Polyangiitis.

Table 2. Frequency of organ involvement in ANCA-associated vasculitides.

Organ involvement	GPA (%)	MPA (%)	CSS (%)
Joints	25	50	28
Upper respiratory tract (e.g. rhinitis, sinusitis)	90	not spec.	47
Asthma	not spec.	not spec.	100
Lower respiratory tract (e.g. infiltrates, nodules, alveolar haemorrhage)	50	35	38
Kidney (glomerulonephritis)	50	80	16
Heart (e.g. myocarditis, coronary arteritis)	10	20	30
Skin (e.g. purpura)	20	70	31
Peripheral nervous system (mono- or polyneuropathy)	20	60	78
Gastrointestinal tract (e.g. ulcers, bleeding)	not spec.	30	33
ANCA pos.	80	75	48

retro-orbital granulomatous masses, and compromised respiratory function may be a sign of subglottic inflammation/stenosis in GPA.

Routine work-up includes blood testing (ESR and CRP, blood count, creatinine and serum electrolytes), urinalysis, ANCA testing and chest X-ray. ENT assessment should be done routinely in GPA and CSS.

Creatinine clearance and 24-hr protein quantification need to be performed if serum creatinine and/or urinalysis are pathological. If there are pathological findings on X-ray, high-resolution CT (HR-CT) and/or bronchoalveolar lavage is used to confirm granulomatous lesions within the airways, alveolar haemorrhage or alveolitis.

MRI of the head is a useful technique to detect sinusitis and granuloma formation in GPA, but there is no agreement as to whether an MRI should initially be done as a routine or only performed if the patients present with symptoms. In CSS, routine assessment also includes lung function testing.

Further diagnostic tests should be performed according to the patient's symptoms (e. g. neurological assessment including EMG and ENG or full cardiac examination).

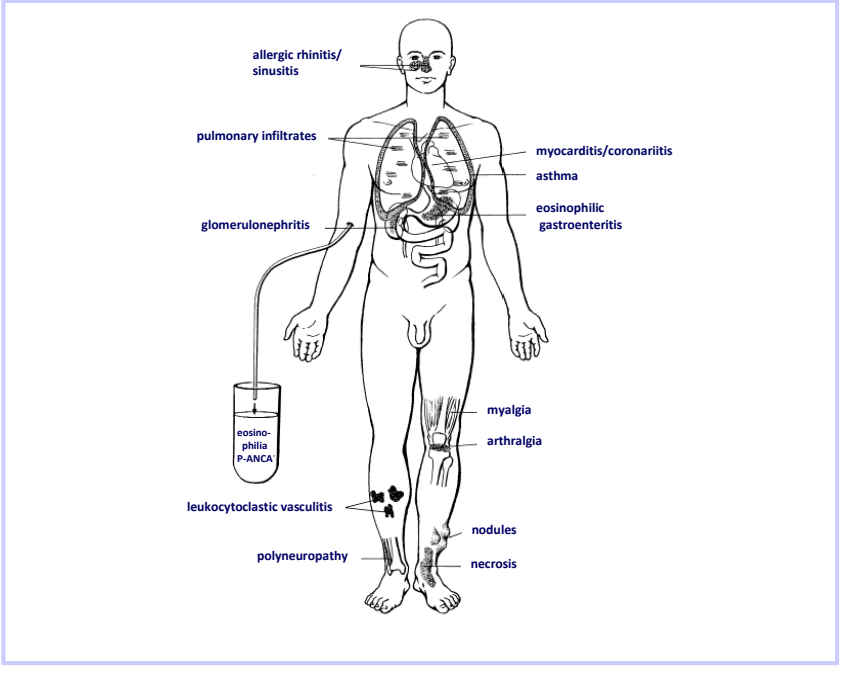

Figure 2. Clinical manifestations of Churg-Strauss-Syndrome.

To confirm the diagnosis, a biopsy from an affected area should be sought (e. g. nasal biopsy, kidney biopsy) at first presentation of the patient.

3 Requirements for family practitioners

If AAV is suspected, the patient should be referred to a rheumatologist/internist. The rheumatologist should screen the patient for organ manifestations and initiate immunosuppressive therapy according to disease stage and activity. After immunosuppressive therapy is introduced, the patient requires monitoring of disease activity and potential side effects of treatment (see below).

Routine blood tests to monitor disease activity include ESR and CRP, blood count, serum creatinine and electrolytes and urinalysis. Creatinine clearance and proteinuria should be assessed regularly in cases of renal involvement. Immunosuppressive therapy may cause bone marrow toxicity with leucopenia/pancytopenia or hepatotoxicity. Regular screening of blood count and hepatic enzymes is therefore needed under most immunosuppressants. Cyclophosphamide can induce haemorrhagic cystitis and bladder carcinoma via its toxic metabolites (such as acroleine). Patients under cyclophosphamide therapy should therefore receive mesna which binds to acrolein.

Blood tests are usually carried out by the family practitioner on a regular basis as recommended by the respective specialist (ranging from once weekly to once monthly). The role of serial ANCA testing is controversial and is usually done at intervals of several months.

Relapse of the disease occurs in 30 to 60 % of patients. In case of recurrent disease activity, the suspicion of relapse or side effects due to immunosuppressive therapy, the responsible specialist should be contacted.

4 Follow up

Patients require immunosuppressive therapy for several years or for life. Patients remain at risk for relapse or opportunistic infections such as CMV reactivation or *Pneumocystis jirovecii*-pneumonia. In some patients, irreversible organ damage occurs if immunosuppressive therapy is introduced too late (e. g. polyneuropathy of haemodialysis due to renal insufficiency).

Follow-up assessments are usually done by the specialist every three to six months and include routine assessment as stated above (blood tests, ANCA, urinalysis, creatinine clearance and assessment of proteinuria) and additional technical diagnostic procedures according to organ involvement and symptoms (e. g. MRI of the skull for retro-orbital granuloma).

Table 3. Treatment of AAV modified from EULAR/EUVAS recommendations.

Disease stage	Recommended treatment
Localised (WG) GPA	**Cotrimoxazole** 2 × 960 mg/day
Early systemic (induction)	**MTX** 15 mg /week s.c. or oral, increase to 20–25 mg/week + GC folic acid substitution
Generalised (induction)	**Cyclophosphamide i.v. or Rituximab (RTX) i.v. + glucocorticoids** **Cyc** 15 mg/kg i.v. for at least 6 times in two to three-weekly intervals **RTX** 375 mg/m2 i.v. 4× in weekly intervals **GC**: prednisolon 1 mg/kg/day for 1 month, taper to <15 mg/day within 3 months
Severe, Crea > 500 µmol/l	standard therapy for generalized disease + plasma exchange
Maintenance of remission	**Azathioprine** 2 mg/kg/day and **MTX** 20–25 mg/week (first choice) **Leflunomide** 20 mg/day duration: at least 18 months
Refractory, Relapsing, Persistent	**IVIG** 2 g/kg for 5 days **Rituximab** 375 mg/m2 weekly for 4 weeks **Infliximab** 3–5 mg/kg i.v. one to two monthly **MMF** 2g/day **15-deoxyspergualin** 0.5 mg/kg/day until nadir; then stop until leucocyte recovery (six cycles) **ATG** 2.5 mg/kg/day for 10 days (adjusted to lymphocyte count)

5 Management

In current treatment recommendations by the EULAR (European League Against Rheumatism), therapy is tailored according to disease stage and activity [4] (Table 3). Life- or organ-threatening disease (e.g. alveolar haemorrhage, extracapillary necrotizing glomerulonephritis) requires remission induction with cyclophosphamide (oral or i.v. pulse) or rituximab and glucocorticoids (initially 1 mg/kg/day). While cyclophosphamide has been the gold standard of remission induction for many years, recent studies suggest that rituximab (4×375 mg/m^2) at weekly intervals is equally effective [5]. Rituximab has been licensed for remission induction for GPA and MPA in the US in 2011. Remission induction is usually needed for three to six months. During this period of time, glucocorticoids should be tapered to less than 10 mg/day (prednisolone). After successful induction of remission, the therapy regimen is switched to maintenance medication such as azathioprine, methotrexate and leflunomide (plus low-dose glucocorticoids). There are no controlled studies evaluating for how long maintenance therapy is necessary. Current guidelines recommend maintenance therapy for at least 18 months. In the US, glucocorticoids are often stopped early (after several months), whereas in Europe glucocorticoid therapy is kept for longer. In severe disease (defined as renal failure with a creatinine $>500\mu$mol/l) plasma exchange is recommended in addition to standard therapy.

In cases of systemic disease without threatened organ function (the so-called early systemic phase of disease), MTX (plus glucocorticoids) is recommended for the induction of remission. Localised disease in GPA (defined as disease limited to the upper and respiratory tract with no systemic symptoms) may be treated with cotrimoxazole to reduce relapses of the upper respiratory tract, probably by controlling nasal *Staphylococcus aureus* infection. Therapy options for refractory disease include rituximab, TNF-antagonists, intravenous immunoglobulins (IVIG), deoxyspergualin and Antithymocyte-globulin (ATG) (Table 3).

6 Diagnostic tests

Anti-neutrophil cytoplasmic antibodies (ANCA) are used as diagnostic markers for the ANCA-associated vasculitides, especially in generalised GPA and MPA, as ANCA is found in a high percentage of these patients. In CSS, ANCA is detected in only 40 % of cases and seems to be correlated to vasculitic manifestations in CSS (such as glomerulonphritis and polyneuropathy). In GPA, ANCA are mainly directed against the neutrophil serine protease proteinase 3 (PR3), whereas in MPA and CSS, ANCA mainly target the neutrophil enzyme myeloperoxidase (MPO).

An immunofluorescence test (IFT) is used as a screening test for the detection of ANCA (Fig. 3). If IFT is positive, an enzyme-linked immunosorbent assay (Elisa) needs to be performed to identify the target antigen of ANCA. Only pro-

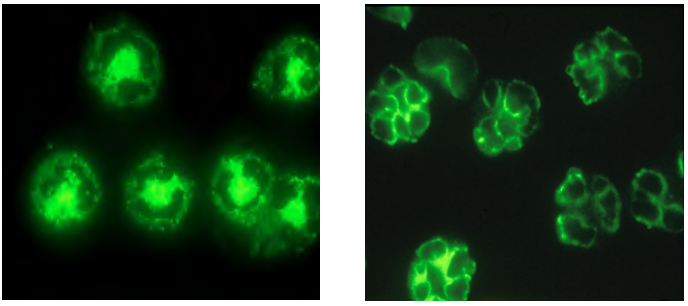

Figure 3. IFT with formalin-fixed neutrophils displaying a cytoplasmatic (left) and perinuclear pattern (right).

teinase 3 (PR3) and myeloperoxidase (MPO) represent common specific target antigens for AAV. Consensus guidelines currently recommend performing an IFT together with an Elisa to detect the ANCA-pattern and the target antigen [4].

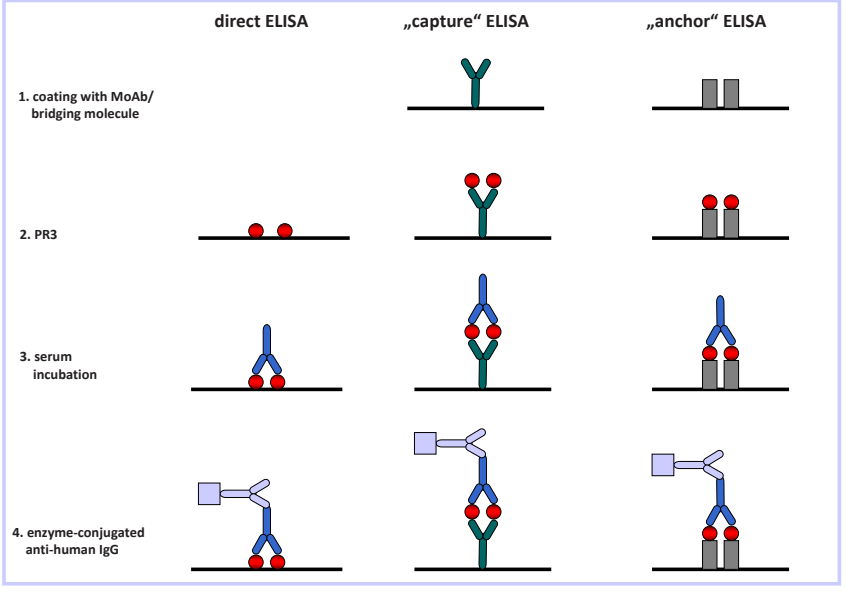

Figure 4. Systematic overview on Elisa procedures for the detection of ANCA directed against proteinase 3.

7 Testing methods

By IFT, two main fluorescence patterns can be distinguished, a cytoplasmic (C-ANCA) and a perinuclear pattern (P-ANCA). Target antigens are detected by enzyme-linked immunosorbent assay (Elisa). Conventional (direct) Elisas using PR3 immobilised to the surface of the Elisa plate, are not standardised and show a great variation in performance and can lack sensitivity as well as specificity, but are still routinely used for the detection of the target antigen of ANCA.

To reduce the covering of possible epitopes by the plastic plate in conventional Elisas, capture Elisa (sensitivity 72–76 %, specificity 100 %) has been developed and is superior in overall diagnostic performance compared to direct Elisa (sensitivity 58–80 %, specificity 95–100 %), however, the sensitivity of capture Elisa may also be reduced by the capturing antibodies, which may also hide relevant epitopes [6]. High-sensitivity PR3-ANCA Elisa (hsPR3-ANCA Elisa) immobilises PR3 via a bridging molecule to the plastic plate, thus preserving all epitopes for the binding of ANCA, and is superior to direct Elisa and capture Elisa in a study testing for PR3-ANCA in patients with GPA [6] (sensitivities and specificities for direct Elisa: 60 % and 99 % respectively, for capture Elisa: 72 % and 99.3 % respectively, for high sensitivity Elisa: 96 % and 98.5 % respectively) (see Fig. 4 for Elisa procedures).

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