ANCA ASSOCIATED VASCULITIS

Major clinicopathologic variants of AAV

- Granulomatosis with polyangiitis (GPA) - ANCA anti-proteinase 3 (PR3) present in >80%
- Microscopic polyangiitis (MPA) - ANCA anti-MPO present in >90%
- Eosinophilic granulomatosis with polyangiitis **(**EGPA)) - ANCA anti-MPO present in 30 to 60%

AAV drug associated:

The most common drugs associated with AAV include:

- Hydralazine
- Propylthiouracil
- Cocaine adulterated with levamisole
- Others include: minocycline, and anti–tumor necrosis factor agents

ANCA anti-myeloperoxidase (MPO) is present

ANCA-negative AAV

Describes cases in which the patient otherwise fulfills the definition for AAV but has negative results on serologic testing for ANCA

- Especially occurs in EGPA but also to some extent in GPA

GPA and MPA overlapping

GPA and MPO have markedly overlapping manifestations and it can be extremely difficult to differentiate between these two diseases.

- There is a growing recognition that ANCA type (anti-MPO or anti-PR3) has more prognostic and clinical meaning rather than the disease type (MPA or GPA)
- Some experts refer to MPO-AAV or PR3-AAV.

Granulomatosis with polyangiitis — GPA

The systems more often affected include the upper and lower respiratory tracts and the kidneys:

The upper respiratory tract

- Rhinosinusitis
- Nasal septal perforation, saddle nose deformity
- Serous otitis

The lower respiratory tract

- Airways
    - Tracheal and bronchial stenosis
        - Subglottic stenosis
        - Most common manifestation of tracheobronchial GPA
        - May be the sole manifestation of GPA and may be severe enough to necessitate tracheostomy
    - Tracheobronchomalacia
    - Tracheoesophageal fistulae
    - Mass lesions
        - Can ulcerate leading to hemoptysis or cause airway obstruction leading to dyspnea and postobstructive infections
    - Bronchiectasis
- Lung parenchyma
    - ILD
        - Commonly UIP pattern, also NSIP and organizing pneumonia

        - Can be seen in GPA, although ILD is more commonly associated with MPA
    - Diffuse alveolar hemorrhage (DAH)
    - Lung nodules/masses

Glomerulonephritis (GMN)

- The typical presentation is that of a rapidly progressive pauci-immune GMN
- May also present with:
    - Asymptomatic hematuria with or without a rise in serum creatinine
    - Variable degree of proteinuria that is usually subnephrotic

Other systems that can also be affected include the skin, neuropathy, and ophthalmic or orbital involvement:

Skin

- Purpura involving the lower extremities is the most common
- May be accompanied by focal necrosis and ulceration
- Others include urticaria, livedo reticularis, and nodules

Ophthalmic or orbital involvement

- Conjunctivitis, corneal ulceration, episcleritis/scleritis, optic neuropathy, retinal vasculitis, and uveitis.
- Orbital inflammation/damage

Neuropathy

- Mononeuritis multiplex
- Sensory neuropathy
- Cranial nerves abnormalities

Extrathoracic tumor-like masses (inflammatory pseudotumors)

- Cases reported most commonly in the breast and kidney

Diagnosis

The diagnosis of GPA is established when autoantibodies directed against PR3 and histopathologic evidence of small vessel vasculitis with or without granulomatous inflammation are present in a patient with a compatible clinical presentation.

- Should be suspected in any patient who presents with constitutional symptoms and clinical evidence of glomerulonephritis or upper or lower respiratory tract involvement
    - The suspicion should be further increased if there is laboratory detection of ANCA
        - ANCA anti-proteinase 3 (PR3) present in >80 % of patients
        - A positive ANCA test strongly supports but does not confirm the diagnosis
        - Both false-positive and false-negative results may be seen
- Biopsy of an affected organ remains the most definitive method to establish a diagnosis and is often required
    - Generally form the kidney, skin, or lung
    - The choice between a lung or kidney biopsy is often debated for patients who present with pulmonary nodules, a positive ANCA, and renal dysfunction but no cutaneous manifestations
        - When pulmonary nodules are peripheral, video-assisted thoracoscopic lung biopsy can be considered
        - Transbronchial biopsies are generally not helpful due to insufficient sample size
        - Patient with progressive renal insufficiency may require a kidney biopsy to fully characterize their kidney disease and guide treatment
        - If the kidney biopsy shows pauci-immune glomerulonephritis, a lung biopsy may not be necessary
    - If sinus disease is extensive, biopsy of involved nasal or sinus tissue usually follows, but may be nondiagnostic
- Common CT findings

    - Multiple pulmonary nodules/masses
        - Generally less than 10 and ranging in size from a few millimeters to 10 cm
        - Approximately 30 to 50 % of nodules are cavitary
    - Ground glass or consolidative opacities that are patchy or diffuse (due to diffuse pulmonary hemorrhage or active vasculitis)
    - Less common findings include UIP, NSIP, organizing pneumonia, bronchiectasis, hilar adenopathy, and pleural effusions
- Bronchoscopy
    - Most common indications
        - To perform biopsy of endobronchial disease
        - To perform BAL. BAL is performed in patients with diffuse parenchymal opacities on HRCT to identify alveolar hemorrhage and rule out infections
        - Transbronchial lung biopsy may identify an alternate diagnosis, but the sample size does not allow for a positive diagnosis of GPA
- Pulmonary function tests
    - PFTs are limited and results depend on the area that is affected
        - The most frequent abnormality is airflow obstruction and may be caused by diffuse airway involvement, focal tracheal or bronchial stenosis or lobar collapse
        - Restrictive process with decreased DLCO if interstitial lung disease present
        - Flow volume loops may show:
            - Flattening of the expiratory loop in patients with intrathoracic tracheal stenosis
            - Flattening of the inspiratory loop in extrathoracic subglottic stenosis when the area of narrowing is still pliable
            - Flattening of both inspiratory and expiratory loops when the airway lesion is tightly stenotic
    - Lung function frequently improves following treatment, although the diffusing capacity may not return to normal
- GPA and MPA overlapping
    - The distinction between GPA and MPA can be difficult
        - Largely based on the presence or absence of necrotizing granulomatous inflammation
            - On biopsy or radiographic surrogates thereof (lung nodules, cavities, or masses)

Treatment

Depends on the presence of an organ or life-threatening condition such as:

- Active GMN
- DAH
- Cerebral vasculitis
- Progressive peripheral or cranial neuropathy
- Orbital pseudotumor
- GI bleeding due to vasculitis
- Cardiac disease due to vasculitis (pericarditis, myocarditis)

Patients with organ or life-threatening condition

Induction treatment

- Glucocorticoids in combination with either rituximab or cyclophosphamide induces remission in the majority of patients, usually within three to six months
    - Methylprednisolone one to three pulses of 1000 mg followed by prednisone 1 mg/kg/d
    - Rituximab (375 mg/m^2 per week for four weeks) or oral cyclophosphamide (2 mg/kg per day)

Maintenance treatment

- Rituximab for most patients who achieve remission after induction
- Azathioprine, methotrexate, and mycophenolate are reasonable alternatives and may be preferred based on other patient-specific factors
- Avacopan*, a* complement 5a receptor (C5aR) antagonist, has been recently approved by the FDA for maintenance of remission in patients with AAV. It is a very effective steroid sparing agent

Duration after remission has been induced

- 12 to 24 months for most patients
- 24 to 36 months for patients with multiple risk factors for relapse
    - PR3-ANCA seropositivity
    - Pulmonary involvement
    - Upper respiratory tract involvement
- Indefinitely if the degree of organ damage was severe and a relapse would be poorly tolerated
- In patients who have had one or more prior relapses who sustained significant organ damage and therefore would not tolerate further injury due to relapse: maintenance therapy indefinitely
- 6 to 12 months for patients with low risk factors for relapse
    - MPO-ANCA seropositivity and no respiratory tract involvement prior to remission

Patients without organ - or life-threatening condition

Induction treatment

- Glucocorticoids combined with methotrexate if the eGFR is ≥60 mL/min per 1.73 m^2 or active GMN
    - Prednisone or equivalent initiated at 0.5 mg/kg/day followed by a reduced-dose glucocorticoid taper
    - Methotrexate initiated at a dose of 15 mg/week, with increases in dose every two to eight weeks of 5 mg/week up to 25 mg/week
- Glucocorticoids combined with Rituximab or azathioprine if the eGFR is <60 mL/min per 1.73 m^2

Maintenance treatment

- Prednisone at 0.5 mg/kg/day (or its equivalent) followed by a reduced-dose taper
- Methotrexate, rituximab, or azathioprine may be continued as maintenance therapy at the same dose used for induction provided that patients have responded to induction therapy.

Patients for whom remission or evidence of progressive improvement is not attained within six months should be considered to have disease resistant to the chosen induction regimen and have their treatment regimen altered.

Microscopic polyangiitis — MPA

Necrotizing vasculitis usually without granulomatous inflammation

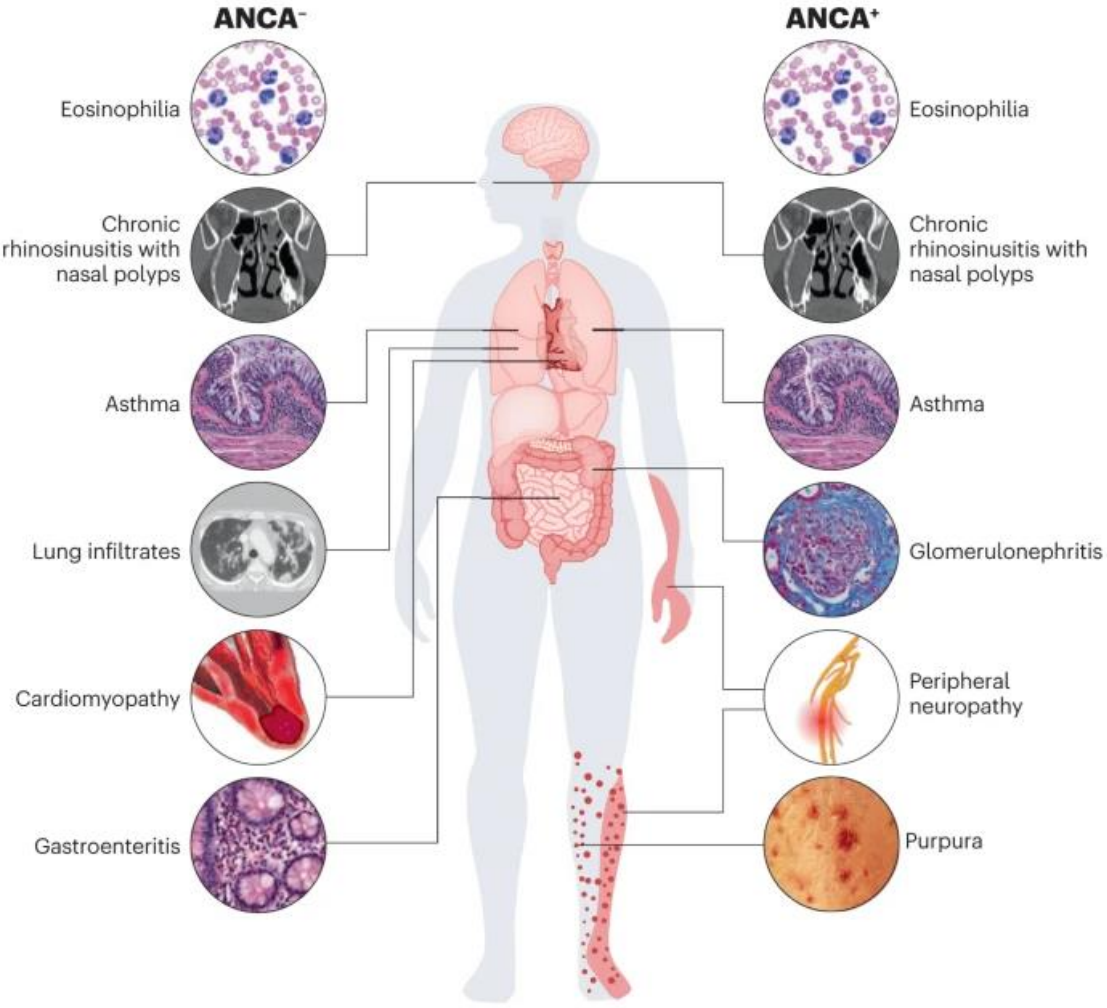
- Primarily affects the lung and the kidneys
    - Necrotizing glomerulonephritis and/or pulmonary capillaritis
- The diagnosis of MPA is established when autoantibodies directed against MPO and histopathologic evidence of small vessel vasculitis with or without granulomatous inflammation are present in a patient with a compatible clinical presentation.
    - ANCA anti-MPO is present in >90 percent of patients
- Diagnostic and treatment approaches are similar to GPA
    - Mycophenolate mofetil can also be used for maintenance of remission in patients with MPA. It is less effective than azathioprine in patients with GPA

Eosinophilic granulomatosis with polyangiitis (EGPA)

Characterized by the combination of asthma, chronic rhinosinusitis, and peripheral eosinophilia (usually >1.500 or >10%) along with granulomatous or vasculitic involvement of several organs.
The clinical manifestations differ on the basis of anti-ANCA status

- Vasculitic features (GMN, peripheral neuropathy and purpura) occur more often in ANCA-positive Eosinophilic features (cardiac involvement and gastroenteritis) are more frequent in ANCA-negative. See figure below taken from *Nature Reviews Rheumatology* 2023;19: 378–393.

Main clinical characteristics of EGPA on the basis of ANCA status



Diagnosis
It should be based on the combination of:

- Highly suggestive clinical features as above
- ANCA-MPO positive in 30 to 60%
- Objective evidence of vasculitis (for example, from histology)
    - Biopsy is recommended when feasible from the more accessible organ, but is not essential to make the diagnosis
        - Vasculitis and eosinophils
        - Lung biopsy is reserved for pts with HRCT infiltrates and no other accessible site

Treatment

Induction

- For *non-severe* disease: corticosteroids: prednisone 0.5 to 1 mg/Kg or equivalent and mepolizumab 300 mg SQ every 4 weeks or benralizumab 30 mg SQ every 4 weeks
- For *severe*-life threatening disease: high dose corticosteroids and cyclophosphamide or rituximab and mepolizumab or benralizumab

Maintenance

- Usually for 12 to 18 months
- Once the disease is under control, the corticosteroid is gradually tapered over 3 to 18 months to the lowest dose to control symptoms
- For patients who received rituximab, cyclophosphamide, or mepolizumab or benralizumab during the induction
    - Continue rituximab every 4 to 6 weeks
    - Cyclophosphamide it should be transitioned to mycophenolate or methotrexate or azathioprine or rituximab
    - Continue mepolizumab or benralizumab every 4 weeks
- Avacopan*, a* complement 5a receptor (C5aR) antagonist
    - First drug approved as the primary indication for maintenance of remission in patients with AAV
    - It is a very effective steroid sparing agent
    - Current approved dose as adjunctive therapy
        - 30 mg p.o. q8h