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1. ANCA- ASSOCIATED PULMONARY VASCULITIS

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ANCA - ASSOCIATED PULMONARY VASCULITIS- A Classification Perspective

The vasculitides are a group of clinically diverse conditions charac. by involvement of blood vessels in an inflammatory, occlusive and often destructive process.

The lungs are affected in isolation or with systemic vasculitis often because of:

1. Large vascular bed
2. Proximity to inhaled antigens
3. Presence of vaso-active cells
4. Versatility of the immune system.

Classification of the vasculitis has been notoriously controversial and a surfeit of systems exists.

These are a group of uncommon diseases and only 500 cases of confirmed Wegener's and 80 patients of Churg-Strauss over a 30 yr period in Mayo Clinic (till 1995) exist. There are about 50 reported histological confirmed cases of Wegener's in India

Classification of the Pulmonary Vasculitis

- A) lung is the major involved organ: Includes WG, Churg-Strauss, microscopic polyangiitis, Necrotizing sarcoid granulomatosis
- B) Lung may be involved: Takayasu's arteritis, Behcet's syndrome, Classic PAN, cryoglobulinemic Vasculitis, Henoch-schonlein purpura.
- C) Part of the spectrum: CT-assoc vasculitis and vasculitis secondary to infection, drugs, or irradiation.

Descriptive (Leibow)

Classic WG
 Limited WG
 Necrotizing sarcoid granulomatosis
 Lymphomatoid granulomatosis
 Bronchocentric granulomatosis
 Churg-strauss

Pathological (Saldana)

lymphocytes depleted, vasculitis
 benign lymphocytic, vasculitis
 malignant lymphocytic, vasculitis
 eosinophilic vasculitis.

Clinicopathological Classification of the Pulmonary Vasculitis

GROUP 1: Distinct Syndromes. Lung Involvement Invariable

Wegener's granulomatosis granulomatosis	lymphomatoid
Necrotizing sarcoid granulomatosis granulomatosis	bronchocentric
Microscopic polyangiitis	Takayasu's
Churg-strauss syndrome	Goodpasture's

GROUP 2: Distinct Syndromes. Nonspecific pathology. Lung Involvement variable

Henoch-schonlein Purpura	R.A
SLE	PSS
Sjogren's	Polymyositis/ dermatomyositis
Hypersensitivity Angitis	Cryoglobulinemia Behcet's

GROUP 3: Vasculitis due to infection.

- A. Specific: bacterial/fungal/ parasitic
- B. non-specific: IE/ Sepsis

GROUP 4: Physical agent induced vasculitis: radiation/ cold

GROUP 5: Overlap syndromes

(Mechanism of Vasculitis)

- **DIRECT INFECTION OF VESSELS**

Bacterial vasculitis (e.g., neisserial)/ Spirochetal vasculitis (e.g., syphilitic)/Mycobacterial vasculitis (e.g., tuberculous)/ Rickettsial vasculitis (e.g., Rocky Mountain spotted fever)/ Fungal vasculitis (e.g., aspergillosis)/Viral vasculitis (e.g., herpes zoster)

- **NONINFECTIOUS IMMUNOLOGIC INJURY**

- a) **Immune complex-mediated vasculitis**

Cryoglobulinemic vasculitis
Henoch-Schonlein purpura
Serum sickness vasculitis
Lupus vasculitis

Rheumatoid vasculitis

Infection-induced immune complex vasculitis (e.g. by hepatitis virus)

Some drug-induced vasculitis (e.g., sulfonamide-induced vasculitis)

Some paraneoplastic vasculitis

Goodpasture's syndrome (mediated by anti-GBM antibodies)

b) Anti neutrophil cytoplasmic autoantibody (ANCA-mediated)

Wegener's granulomatosis

Microscopic polyangiitis

Churg-Strauss syndrome

Some drug-induced vasculitis (e.g., thiouracil-induced vasculitis)

c) Cell-mediated vasculitis

Giant cell arteritis

Takayasu's arteritis

Kawasaki disease

The anti-neutrophil cytoplasmic antibody:

1. Role in diagnosis

Seminal work in this field was done by Davies and Van der Woude. The observed patterns are an artifact of ethanol fixation due to re-distribution of MPO. The Patterns on IIF are referred to as C-ANCA & P-ANCA. The Corresponding antigens are varied.

Wegener's granulomatosis	C-ANCA (75%-80%)	PR3
	P-ANCA (10%-15%)	MPO
	Negative (5%-10%)	
Microscopic polyangiitis	C-ANCA (25%-35%)	PR3
	P-ANCA (50%-60%)	MPO
	Negative (5%-10%)	
Churg-Strauss syndrome	C-ANCA (25%-30%)	PR3
	P-ANCA (25%-30%)	MPO
	Negative (40%-50%)	

BIOLOGICAL ACTIVITIES OF PR3

Regulation of differentiation

- Truncation of NF- κ B
- Hydroxylation of Hsp 28
- Truncation of Sp126
- Component of leukemia-associated inhibitor

Impact on cytokine network

- Conversion of IL-8 to active form
- Conversion of TNF- α to active form
- Conversion of IL-1 β to active form
- Activator of latent TGF β
- Enhances IL-8 production by endothelial cells

Other substrates and physiological functions

- Cleavage of C1 inhibitor
- Cleavage and inactivation of the thrombin receptor
- Cleavage of matrix macromolecules (elastin, fibronectin, laminin, vitronectin, type IV collagen)
- Activator of MMP-235

Effect on endothelial cells

- Internalization into cells
- Induction of apoptosis
- Activates signaling molecules
- Stimulates tissue factor production

BIOLOGICAL ACTIVITIES OF MPO

Bactericidal through enzymatic production of hypochlorous acid.

- Functions as a peroxidase to produce free radicals causing lipid peroxidation of low-density lipoproteins
- Produces oxidants that activate cell-signaling pathways
- Produces hypochlorous acid; activates NF- κ B transcription factor
- Produces advanced glycation end products at site of inflammation
- Internalized by endothelial cells causing increased free radical production

- Tyrosine nitration of vascular ECM proteins

Problems in ANCA interpretation

A) IIF

1. Only typical patterns have diagnostic value.
2. Poor inter-observer reliability.
3. Confusion between ANA and p-ANCA interpretation.

B) ELISA.

1. As sensitive as IIF testing
2. De-naturing of target antigen causes false-ve
3. Commercial kits fare poorly in sensitivity.

Assuming a prevalence of 20%, the PPV of C-ANCA is 66% and p-ANCA is 30%

1. Wegener's granulomatosis

The Estimated prevalence of WG is 13-30 cases per million /5-years. From 1979-88, WG was listed as the cause of death in 1784 death certificates in the U.S. Its Peak incidence in the 4.th- 6.th decades of life and has no gender predominance

Godman and Churg criteria for Wegener's- the Wegener's triad (1954)

1. Necrotizing granulomatous inflammation of the upper and lower airways.
2. Generalized focal necrotizing vasculitis involving both arteries and veins.
3. focal necrotizing glomerulonephritis

American College Of Rheumatology classification for Wegener's

≥ 2 of the following criteria

1. Urinary sediment with RBC casts or >5 RBC'S/ hpf.
2. Abnormal findings on the chest radiography (nodules, cavities and fixed infiltrates)
3. Oral ulcers or nasal discharge
4. Granulomatous lesion on biopsy

1. Granulomatous phase without vasculitis will be missed!!

2. Classification criteria only-not a diagnostic formulation

Upper airways are involved in 90% of WG

Nasopharynx is involved in 60-80%. Presentation is with epistaxis, septal perforation, nasal congestion/ pain, mucosal ulcers or strawberry gingival hyperplasia. Saddle nose is the characteristic deformity and is seen in 10-25%; Reconstruction has a 92% success in most centers.

Ear involvement is seen in 30-50% with Chr. Sinusitis, Chr. Mastoiditis & Hearing loss. The latter can be due to:

- | | |
|----------------|---------------------------|
| Active disease | a. middle ear destr.n |
| | b. vasculitis of cochlea |
| Infection | c. CSOM |
| | d. TM perforation |
| Sequelae | e. granulation in mastoid |

Sinus involvement is common presenting as Chr. Sinusitis. CT is useful > 85% showing thickening/clouding sinuses in 75% and erosion/ destruction of bones 25-50%

Airway involvement in Wegener's:

Stenosis occurs in 10 to 30% of patients with WG. Symptoms are nonspecific. Presentation is with dyspnea, wheezing, stridor, and change in voice. Concomitant involvement of the Nasopharynx or sinuses is the rule (97%). It may develop years after the initial diagnosis of WG with inactive disease. The site of tracheal stenosis is usually circumferential and localized, extending 3 to 5 cm below the glottis. Extensive endobronchial abnormalities were noted in 11 patients with Normal CxR. Flow-volume loops may be insensitive and FOB is a must in all. Circumferential narrowing of the trachea due to a mature scar was observed in 20 (74%) cases; friability or acute inflammation was noted in only seven patients (26%). The impact of medical therapy in altering the course of endobronchial WG is not clear. Aggressive immunosuppressive therapy is warranted when an active inflammatory component is demonstrable. Disease localized to the airways may not respond to medical treatment.

In this circumstance, alternative treatment modalities include CO2 or Nd: YAG laser, Dilatation ±intratracheal CS injections, placement of Silastic airway stents, tracheostomy, Laryngeal-tracheal reconstruction, and partial tracheal resection.

Surgical intervention or manipulation of the airways is minimized during flares. Intralesional injection with long-acting CS and intratracheal dilatation is efficacious in treating SGS. Long-term follow-up by an otolaryngologist is essential to monitor response.

Radiology of Wegener's:

The most common finding are Multiple nodules from 0.3 -10 cm in diameter and are usually bilateral. They are usually smooth or spiculated. 50% eventually cavitate esp. > 2 cm in diameter. Cavities in Wegener's typically have thick walls and shaggy, irregular inner borders.

In a study by Lee KS et al, 27 (90%) had nodules or masses. Cavitation >1 nodule was present in 13 (48%) of these 27 patients. The nodules ranged from 1 to 32 in number (mean 8) mostly sub pleural or peribronchially. Also common was air space consolidation or GGO. These were seen in 50% as diffuse, wedge-shaped pleural based, peri bronchial and patchy. Diffuse consolidation or GGO was seen in 8% & usually DAH. Pleural effusions were seen in 12 to 25%. They may be unilateral or bilateral, small or large. Other Features that can rarely pleural thickening, Pneumothorax (PTx), hydroptx, or pyoptx. Mediastinal lymph node enlargement is seen in 20% of patients.

Surgical lung Biopsy (SLBx) is optimal to establish a firm diagnosis of pulmonary WG. Vasculitis and necrotizing granulomas are found on SLBx in >90% of patients. Micronecrosis or containing neutrophils and mononuclear cells appear to be early lesions. Later findings include geographic necrosis, granulomatous infiltration, vasculitis, and varying degrees of fibrosis.

SLBx in pulmonary WG (n=87)	Travis. Am J Surg Pathol 1991; 15:315-333
Vascular inflammation (acute or chronic)	94%,
Parenchymal necrosis	4%,
Scattered giant cells	9%
Areas of geographic necrosis	9%
Granulomatous micro abscesses with giant cells	69%
Neutrophilic micro abscesses	5%
Poorly formed granulomas (59%), capillaritis	31%
Fibrinoid necrosis	11%

Granulomatosis: Goals of treatment for Wegener's

1. Patient survival
2. Induce remission of active disease

3. Reduce disease relapse
4. Minimize therapeutic toxicity
 - a) Use the least toxic yet effective treatment option
 - b) Actively pursue strategies to prevent and monitor for toxicity
 - c) Use treatment regimens at doses and schedules on which there data

Current therapies, though effective in inducing remission, are poor in reducing relapses and high in toxicity

Challenges in conducting therapeutic trials in Wegener's granulomatosis include

1. Rarity of Wegener's granulomatosis
2. Potential for active disease to be life threatening
3. Available treatment of established efficacy
4. Definition of outcome measures
5. Imprecise means of assessing active disease
6. Extended follow-up is necessary to fully assess relapse and to reach study endpoints

Management of Wegener's is according to stage of the disease.

1. Localized disease:

WG affecting the upper or lower respiratory tract alone without constitutional disturbance is treated as localized disease. It has been treated with prednisolone alone or with the antibiotic combination, Co-trimoxazole.

Role of Septran (T/S) in Wegener's

De Reme reported in 1985 that improvement in 11 of 12 patients with WG occurred with T/S. Possible modes of activity include:

1. Anti-inflammatory & inh. of formation of O₂ radicals by activated neutrophils.
2. Antimicrobial effects and inhibition of *S. aureus* driven proliferation of T lymphocytes and B lymphocytes, immunoglobulin and cytokine production.

T/S has been found in several reports to be beneficial in limited WG. Interpretation of these results is however confounded by

1. Their retrospective nature
2. by the use of concurrent immunosuppressive agents

3. By the difficulty in defining active upper airways disease, and
4. by the lack of controlling for infection.

Two prospective studies found no role in limited WG. A study on a Maintenance regime by Stegman (NEJM 96) found it useful only in URT flares. It is never to be used alone in systemic vasculitis. T/S is used always in patients on CYS as PCP prophylaxis.

2. Early systemic disease

Comprises

- A. localized WG with constitutional disturbance

Or

- B. WG which is multi-focal but without threatened organ function.

Cyclophosphamide & steroids have been standard therapy. Several uncontrolled studies have reported disease remission in 60-70% with Methotrexate and steroids used for induction therapy.

Role of Methotrexate in Wegener's:

Methotrexate may be used in Wegener's as:

1. Induction therapy
2. Maintenance therapy.

Remission maintenance in WG:

In a NIH (n=32) trial with a F/U of 31 months found a CR 100% with no deaths and relapse rate of 16%. Thus Methotrexate has a role in remission maintenance in WG as an alternative to Cyclophosphamide and azathioprine

Induction therapy:

The control of early renal vasculitis, with normal or modest creatinine elevation with Methotrexate is more controversial. Two studies have reported stabilization of excretory function; others have found renal vasculitis to predict refractory, progressive disease after Methotrexate. Inability to reduce the steroid dose and relapsing disease have been predictive of more widespread vasculitis after methotrexate Therapy.

In the NORAM trial, 100 newly diagnosed patients with S. Cr <150mol/l and no life or organ-threatening involvement randomized to Mtx and Cyc. At the primary endpoint (remission at 6 m), equal remission (MTX 89.8% vs CYC 93.5%) was noted. However, the relapse rate at 1 yr was unacceptably high (69.5% MTX and 45% CYC) in the Mtx arm. The mean time to relapse was 13.5 months.

1. INDUCTION.COMPARISON OF THREE STUDIES OF METHOTREXATE AND PREDNISONE IN WEGENER'S GRANULOMATOSIS

	Sneller et al (1995)	de Groot et al (98)	Stone et al 99
Total number	42	17	19
MTX/PRED as initial regimen (%)	36	65	100
> 3 organs at start of treatment (%)	60	NA *	74
GN at start of treatment (%)ANCA(%)	50	12	47
ANCA (%)	83	76	84
Max MTX dose/week	25.0 mg	0.3 mg/kg	22.5 mg
Route of MTX	Oral	Intravenous	Oral Starting
PRED dose	1 mg/kg/d	10 mg/d (median)	40
PRED tapered to QOD	Yes	No	No
Improved (%)	83	59	89
Remission (%)	71	35	74
Developed GN on treatment (%)	2	29	55
Relapse (%)	27	33	0
Deaths (%)	7	0	0
Hepatotoxicity (%)	24	0	32
Opportunistic infections (%)	10	0	0
MTX pneumonitis (%)	7	0	0
Leukopenia (%)	7	0	0

*Patients with fulminant disease may receive intravenous methyl prednisone (1 g/d for 3 days) at the start of corticosteroid therapy. For patients with limited disease, the initial dose of corticosteroids may be lower (e.g., 0.5-0.8 mg/kg/d).

Cyclophosphamide for Generalized Wegener's :

Data from historic controls show the marked improvement in disease remission induction with CYC.

Current remission rates are 75-90% but relapse rates are still 50%. This is at expense of marked toxicity.

COMPARISON OF TWO LARGE WEGENER'S GRANULOMATOSIS COHORTS

	Bad Barmstedt (N +155)	NIH(N=158)
Median follow-up (years)	7	8%
Patients taking CYC/CS	92%	84%
MESNA use	Yes	No
Alternate-day corticosteroid tapering	No	Yes
Complete remission achieved	54%	75%
Relapses (after complete remission)	60%	50%
Overall mortality	14%	20%
Mortality (2 to WG or treatment)	14%	13%
Serious infections	12%	46%
Deaths as a result of infection	26%	3%
Myelodysplasia	3%	2%
Cyclophosphamide-induced cystitis	8%	43%
Bladder cancer	12%	3%
	<1%	

3. Generalized/renal disease

In 1985, Walton found that WG had 82% mortality at 1 yr. (median 5 mo). In 1970s high dose CS improved survival to 12.5 months. However a NIH cohort of 57 patients in 70-90's showed that 45 developed progressive GN on steroids & 17% remission, mostly that of limited WG. Hence CS are never used alone in WG

A 6-MONTH CORTICOSTEROID TAPER

Initiate treatment with 1 mg/kg/d of prednisone for the first month up to a max of 80 mg/d.

After 1 month, prednisone is tapered by 10 mg/wk. The goal is to achieve a dose of 20 mg/d by the end of 8 to 10 weeks of therapy.

Then, maintain dose of 20 mg/d for 2 weeks.

Then, reduce dose by 2.5 mg/wk until a dose of 10 mg/d is reached.

Then, reduce dose by 1 mg/wk until off.

Cyclophosphamide (Cyc) is a powerful agent with good remission rates but has unacceptable toxicity in the long run. Some of these (gonadal, bladder Ca, MDS/ Leukemia) are dose dependent

PROTOCOL FOR USING CYCLOPHOSPHAMIDE SAFELY

Limit duration of CYC use (ideally 3-6 months for remission induction)

Take medication in morning; Drink eight 8-oz glasses of water daily

Adjust dose to maintain white blood cell count greater than 4000 mm³

Check complete blood count every 2 weeks and a urinalysis monthly

Adjust dose for renal dysfunction (see algorithm below)*

Always use Pneumocystis carinii prophylaxis

Long-term surveillance for CYC-induced bladder injury (annual urinalyses, with cystoscopy as indicated by hematuria or abnormal cytologic findings)

Creatinine Clearance (mL/min)	CYC Dose (mg/kg/d)
>100	2.0
50-99	1.5
25-49	1.2
15-24	1.0
<15 or on dialysis	0.8

This result is multiplied by a factor of 0.8 for women.

Recent studies have aimed to reduce exposure

- A. by using pulse rather than continuous administration or
- B. by switching to an alternative drug once remission has been obtained

APPROACH A. PULSE Cyclophosphamide

The 11 non-randomized studies have comprised of 202 patients on pulse CYC. Pulses of CYC were given at doses of 375–1000 mg/m² per pulse at 1- to 4-week intervals with variable steroid and adjuvant therapy regimens. Remission was achieved in 112/191 evaluable patients. Relapse occurred in 68/135 patients. Leucopenia, infection, hemorrhagic cystitis and death were rare. A meta-analysis done concluded that remission rates were comparable but pulse Cyclophosphamide had significantly lower infection rates & higher relapse rates. The CYCLOPS study is currently comparing the efficacy of daily oral to pulsed Cyclophosphamide for renal vasculitis in 160 patients

Strategy 2: use of Azathioprine as maintenance

The CYCAZAREM trial compared AZA and CYC for maintenance of remission in patients with moderate renal involvement (cr<500 mol/l). 155 patients with AAV (both WG & MPA) studied. 119(77%) achieved remission by 3 months. There were seven deaths during the induction phase and one withdrawal. There was no difference in relapse rates (15.5% in the AZA group and 13.7% in the CYC gr. up to the end of the study at 18 months after treatment outset. This suggests that CYC can be safely withdrawn following induction of remission. The REMAIN study is evaluating the optimum duration of therapy.

Severe renal disease:

The delayed diagnosis of renal vasculitis increases the risk of the development of renal failure by the time of presentation. Progression to ESRD is not inevitable, and

recovery is possible in many. The addition of pulsed MP or PE or both to standard Rx has been advocated to increase the chances of renal recovery. A pooled analysis of existing data suggests that plasma exchange may be superior in this regard but numbers are small and inclusion criteria and immunosuppressive regimens varied

TRIALS	No.	Plasma exchange	No plasma exchange
Glockner	12	5/8	3/4
Pusey	19	10/11	3/8
Cole	11	3/4	2/7
Levy	20	9/11	5/9
Guillevin	8	4/6	1/2
Haubitz	22	6/12	2/10
(Jayne)†	26	9/16	4/10
Total		46/68 (67%)*	20/50 (40%)

The MEPEX trial is comparing the rates of renal recovery for those with an initial creatinine over 6 mg/dl between the addition of 3 g of mp and 7 PE, in addition to standard Rx. Preliminary data suggest that renal outcome was better in the plasma exchange-treated group in overall rate of dialysis-free survival. Death rates were similar in the two groups. These results were maintained at the 1-yr follow-up

Plasma exchange aims to

- a) deplete circulating pathogenic auto-antibodies;
- b) other effects, such as the removal of cytokines,
- c) complement, and coagulation factors, and less well-defined
- d) immuno-regulatory phenomena may also contribute

Other newer experimental agents are being tried in AASVC. Data for most exists only as case reports or as small series. None have an established role in AASVC as of now and are being tried in resistant disease or to decrease the toxicity seen with conventional regimes. These agents include:

1. Mycophenolate mofetil.
2. leflunamide
3. IVIG
4. Deoxyspergualin
5. Cyclosporine.
6. Anti-TNF inhibitors
7. Rituximab.

Editorial Comments :

Pulmonary vasculitides are a group of relatively rare disorders that affect multiple systems other than the lungs. These groups of diseases are being recognized more and more in this country. Most of the time they are confused with other diseases like tuberculosis, pneumonia for cancer. A high index of suspicion is required to diagnose these conditions. A number of diagnostic tests including ANCA are required to arrive at diagnosis. Untreated, the condition is FATAL. However, response to immuno suppressive drug is quite effective, although not universally.

ANCA associated Pulmonary Vasculitis

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