VASCULITIS - A DIAGNOSTIC APPROACH

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Objectives

• To summarise key points relevant to vasculitis for the physician

• To outline a diagnostic approach

• To review the use of ANCA
• The vasculitidies are mixed group of uncommon diseases characterised by inflammation & necrosis of blood vessels

  – Primary vasculitis

  – Secondary vasculitis
• Primary vasculitis:-
  – occurs in absence of recognised precipitating cause/associated disease

• Secondary vasculitis
  – secondary to established disease
  – secondary to infection
  – secondary to malignancy
  – secondary to drugs
• Consequence of vascular inflammation depends on size/location/number of blood vessels involved

• May be relatively indolent with disease isolated to single organ/vessel or rapidly fulminant multi-system disease
• Muscular arteries may develop segmental or focal lesions
  – segmental
    • affects whole vessel circumference
    • stenosis/occlusion of vessel
    • results in infarction of distal organs
  – focal
    • may lead to aneurysm formation
    • aneurysms may rupture
• Untreated disease has poor prognosis with 5 year survival of 10%

• Major advances in treatment have improved survival

• mortality and morbidity from disease & treatment remain high
Epidemiology

Overall annual incidence rates of systemic vasculitis estimated at 40 per million

- Giant cell arteritis most common
  - 180 per million adults >50 years per annum
- Wegner's granulomatosis
- Microscopic polyangiitis  3-8/ mill pa
- Churg-Strauss syndrome
- Takayasu arteritis/classical PAN very rare
  0-1.5/million
Classification of Systemic Vasculitis

- Classification is confusing & controversial
- Considerable overlap
- Underlying cause usually unknown
- Different types of vasculitis syndromes can be associated with specific causes
  - Hepatitis B
    - PAN
    - Cutaneous vasculitis
    - Cryoglobulaemia
    - GN
• 1990 ACR developed classification

• 1994 Chapel Hill consensus conference devised definitions for nomenclature based on:

1. Clinical & laboratory features

2. Size of involved vessels
• Alternative systems include classification based on:-
  – size of dominant vessels involved
  – known aetiological factors
  – ANCA

• None provide diagnostic criteria or address the problem of incomplete variants of the disease

• For majority of vasculitidies specific diagnostic tests are lacking and diagnosis must be based on size of vessel involved and associated non-specific clinical and laboratory findings
**Diagnostic Approach**

- Should be suspected in any patient with multi-system disease not readily explained by infection or malignant process.

- Rarely clear at outset that vasculitis is the cause.

- Establishing diagnosis consists of:
  1. Documenting that vasculitis is present.
  2. Defining to fullest degree the possible vasculitic syndromes that are responsible.
• Differentiation of various syndromes is important
• Some vasculidities are relatively benign & self limiting eg:
  – HSP
  – Drug induced reactions
• Many vasculidities are potentially lethal and require early use of high dose immunosuppression
• Others require very different approaches eg
  – Infective endocarditis
  – Atrial myxoma
• Diagnosis must first be suspected for appropriate treatment to be arranged

• Much is known about pathogenesis of some vasculidities eg. SLE

• Early diagnosis may lead to serologic identification of patients at risk of certain clinical presentations
Diagnostic approach

1. Complete History & Physical Examination
   • Symptoms suggestive of systemic vasculitis

Systemic

- malaise, fever, wt loss
  myalgia, arthralgia

Skin

- purpura (palpable)
  ulceration, infarction
ENT
- epistaxis, crusting
  sinusitis, deafness

Resp
- cough, wheeze
  haemoptysis, dyspnoea

Cardiac
- chest pain, SOB
GI
- mouth ulcers, abdo pain, diarrhoea

Neuro
- sensory/motor impairment
- Many syndromes are based on clinical rather than lab criteria

- Principle historical & clinical features help to distinguish the major vasculitic syndromes
• Initial evaluation should include detailed history of:
  
  - drug exposures
  
  - risk factors for Hep B/C/HIV
  
  - history of valvular heart disease
  
  - features that identify underlying Rheumatic disease (eg SLE/APS)
But what to ask?

Think in terms of disorders
• Any :- asthma
    sinus problems
    nose bleeds
    deafness
    haemoptysis
    pins / needles
• Any :- skin rash
  photosensitivity
  mouth ulcers
  hair loss
  dry / gritty eyes
  dry mouth
  Raynauds
  pleuritic pain
  blood clots
  miscarriages
• Any: - weight loss
  fevers
  night sweats
2. **Laboratory Investigations**

- Directed towards establishing
  - diagnosis
  - organs affected
  - disease activity
Assessing Inflammation

- Blood count & differential
  - total WCC
    - leucocytosis consistent with infection & primary vasculitis
  - leucopaenia associated with CTD’s
  - eosinophils
    - elevated in CSS, drug reaction
Assessing Inflammation (cont)

- Acute phase response
  ESR/CRP

- Liver function- often non specific
  - may also suggest viral infection
Assessment of organ involvement

- Urine analysis
  - proteinuria
  - haematuria
  - casts

- Renal function
  - creatinine clearance
  - 24hr protein excretion
  - biopsy
Assessment of organ involvement

Chest radiograph

- Liver function

- Nervous system - NCS

- Cardiac function - ECG
  - Echo

- Gut - Angiography
**Immunological Tests**

- Anti-neutrophil cytoplasmic antibodies
  - proteinase 3
  - myeloperoxidase
- Other autoantibodies
  - Rheumatoid factor
  - ANA nuclear antibodies
  - Antibodies to extractable nuclear antigens
  - Anti ds DNA
  - Anticardiolipin
Immunological Tests

• Complement - levels are low in SLE and infection but high in primary vasculitis

• Cryoglobulins
**Differential diagnosis**

- Important to exclude infection and other conditions that may present as multi-system disease & mimic vasculitis
- Blood cultures
- Viral serology
- Echo cardiography
Specific Investigations

- Imaging of sinuses

- Biopsy of affected organs eg. skin/kidney/temporal artery
  - necessary to confirm diagnosis
  - preferably taken prior to high dose immunosuppression
  - yield is directly proportional to evidence of involvement of specific tissue
  - skin biopsy should be reserved for when diagnosis is unclear
Important Mimics of Vasculitis

• Infective Endocarditis

• Atrial Myxoma

• Cholesterol embolism

• Antiphospholipid antibody syndrome

• Vasoconstrictive drugs eg. ergot poisoning
Anti-Neutrophil Cytoplasmic Antibodies

• Diagnosis & classification of vasculitis has been revolutionised by discovery & characterisation of ANCA

• Detected in serum by indirect immunofluorescence using ethanol fixed human polymorphs

• Confirmatory testing uses solid phase ELISA assays for defined target antigens
• 2 main staining patterns
  – cytoplasmic C ANCA
  – perinuclear P ANCA
• Highly specific markers for several systemic vasculidities
  – Wegners Granulomatosis
  – microscopic polyangitis
  – Churg-Strauss syndrome
  – idiopathic pauci-immune necrotising & cresenteric GN
• Only moderately sensitive in limited or localised disease
- c ANCA correlates with proteinase 3 specificity
  - most frequently observed in WG
  - sensitivity for active WG approx 90%
  - can be found in other systemic vasculitis although p ANCA more common

- Anti PR3 ANCA may have role in disease pathogenesis in WG probably by enhancing disease expression

- In stable WG patients a rise in c ANCA may herald a clinical exacerbation
• p ANCA in most cases induced by antibodies against myeloperoxidase (MPO)
  - less specific than c ANCA
  - Anti MPO antibodies occur in:–
    • necrotising GN (65%)
    • microscopic polyangitis (45%)
    • CSS (60%)
    • Wegners (10%)

  - can also occur in other conditions
    but target antigen rarely MPO
    • RA
    • IBD
    • Malignancy Infection
Conclusions

- Vasculitis should be considered in patients with multi-system disease

- Classification can be difficult

- Investigation should aim to
  - Establish diagnosis
  - Assess organ involvement
  - Assess disease activity
  - Identify causes of secondary vasculitis
  - Exclude vasculitis mimics