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 vasculitides 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
- Wegners granulomatosis}
- Microscopic polyangitis } 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