VASCULITIS
AN APPROACH AND REVIEW

Stuart S Leicht, MD, FAAD, FACP
Professor of Medicine
Chief, Division of Dermatology
Quillen College of Medicine

Disclaimer
NEITHER THE PUBLISHER NOR THE AUTHORS ASSUME ANY LIABILITY FOR ANY INJURY AND OR DAMAGE TO PERSONS OR PROPERTY ARISING FROM THIS WEBSITE AND ITS CONTENT.

CONFLICTS OF INTEREST

- NONE

Vasculitis: definition

- Vasculitis is a disease process characterized by inflammation, necrosis and hemorrhage of blood vessels and whose signs and symptoms are attributable to tissues and organs damaged by compromised vasculature. This damage is mediated by ischemia, thrombosis and spread of inflammation to adjacent tissue.
- It can occur PRIMARILY or may be SECONDARY to many systemic disorders.
- It may be restricted to the skin or involve other organ systems additionally or exclusively.
CLASSIC PRIMARY VASCULITIDES

- Leukocytoclastic vasculitis (hypersensitivity)
- Wegener’s granulomatosis
- Microscopic polyarteritis
- Churg-Strauss syndrome
- Polyarteritis nodosa
- Temporal arteritis, (giant cell arteritis and polymyalgia rheumatica)
- Takayasu’s arteritis
- Kawasaki disease

DIFFERENTIAL DIAGNOSIS

VASCULITIS VS VASCULOPATHY

A vasculopathy may be defined as a dysfunction or nonimmunologic injury of small blood vessels or capillaries that leads to local vascular insufficiency, thrombosis and sometimes SECONDARY vascular inflammation. They are common and may clinically resemble vasculitis and therefore must be clinically differentiated. They also may be valuable clues to other serious processes in their own right.

PHYSICALLY INDUCED VASCULOPATHIES

- Cholesterol emboli
- Thromboembolism
- Atrial myxoma
- Temperature induced injuries
  - Erythema ab igne
  - Perniosis
  - Frostbite
- Foreign material injection
- Cryofibrinogenemia
- Calciphylaxis
- Ionizing radiation
- Severe hypertension
Schamberg’s disease (progressive pigmented purpura)
Purpura annularis telangiectoides
Lichenoid dematosis of Gougerot and Blum
Lichen aureus
THROMBOTIC VASCULOPATHIES

- Atrophie blanche
- Factor C or S deficiency
- Factor V Leiden and others...
- Thrombotic thrombocytopenic purpura
- Type I (possibly also II and III) cryoglobulinemia
- Antiphospholipid antibody syndrome
- Lupus anticoagulant
- Anticardiolipin syndrome
- Coumarin necrosis
- Purpura fulminans (DIC)
- Trousseau’s syndrome
- Hyperacute transplant rejection
- Thromboangiitis obliterans (Buerger’s disease)
SEPTIC VASCULITIS

- Rickettsia sp
- Neisseria sp
- Treponema pallidum
- Herpes simplex
- Herpes zoster
- Cytomegalovirus
- Echovirus
- Coxsackie virus
- HIV
- Parvovirus
- Borrelia burgdorferi
- Leptospirosis
- Escherichia coli-induced hemolytic uremic syndrome or TTP
- Bacterial septic emboli e.g. SBE
CUTANEOUS VASCULITIS

MANIFESTATIONS

BY ANATOMY

- Postcapillary venules or arterioles:
  - **Palpable purpura**
  - Superficial ulcers
  - Vesicles or Pustules
  - Urticaria and angioedema
  - Erythematous plaques
  - Sweet’s-like lesions
  - Splinter hemorrhage
CUTANEOUS VASCULITIS MANIFESTATION BY ANATOMY

- Deep dermal or subcutaneous small arteries:
  - Deep ulcers
  - Infarcts
  - Livido reticularis
  - Nodules
VASCULITIS MORPHOLOGY

ARTERIES
Larger “named arteries” usually present with regional ischemia, pulselessness and occasionally with nodules and dramatic ulceration

CONFUSING CLASSIFICATIONS AND SCHEMAS

BY:

- Clinical syndrome
- Size and type of vessel involved
- Inflammatory pattern e.g. granulomatous or not
- Other disease diagnoses
- Laboratory immune markers and abnormalities
- Organs and tissues involved
- Immune mechanism, type of inflammatory cells

MY SCHEMA, (LEICHT’S)
GROUND RULES

- A primary vasculitis can be classified on the basis of the LARGEST documented involved vessel, NOT the most predominant and by the presence or absence of granuloma.
- In general, any pattern of smaller vessels can accompany the largest distinctive vessel involved
- The glomerulus may be regarded simply as a specialized arteriole
The tissue pathology, clinical findings, laboratory tests and spectrum of organ involvement in these disorders is often not sufficient individually to readily allow distinguishing among these illnesses. It is the total picture of all the findings and the pattern of prominent vessel involvement that usually allows assignment of a diagnosis and treatment. To add to the challenge, some patients have only partial or limited expression of the classical syndromes or overlap features of two or more diseases.
**HISTOLOGIC CLASSIFICATION**

<table>
<thead>
<tr>
<th>VESSEL SIZE</th>
<th>WITH GRANULOMA</th>
<th>NO GRANULOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LARGE</td>
<td>YASUDA'S ARTERITIS, GIANT CELL ARTERITIS</td>
<td></td>
</tr>
<tr>
<td>MEDIUM</td>
<td>CHURG-STRAUSS SYNDROME, WEGENER'S GRANULOMATOSIS</td>
<td>POLYARTERITIS NODOSA</td>
</tr>
<tr>
<td>SMALL</td>
<td>MICROSCOPIC POLYARTERITIS</td>
<td></td>
</tr>
<tr>
<td>CAPILLARIES, ARTERIOLES</td>
<td>LCV</td>
<td></td>
</tr>
</tbody>
</table>

**LEUKOCYTOCLASTIC VASCULITIS**

- Lower extremity/dependent palpable purpura
- Histopathologic criteria
- Infiltration of the vessel wall with neutrophils and presence of leukocytoclasis (nuclear dust).
- Vascular wall injury:
  - Endothelial swelling, nuclear pyknosis
  - Fibrinoid changes in the wall
  - Necrosis
  - Hyaline thrombosis and fibrosis secondary to earlier vessel damage
- Other: intense edema, **RBC extravasation**, immunoglobulin and complement components in the vessel wall.

**LEUKOCYTOCLASTIC VASCULITIS**

*Idiopathic (primary)*

**Distinctive variant syndromes:**
- Henoch-Schönlein purpura
- Urticarial vasculitis, hypocomplementemic and normocomplementemic
- Erythema elevatum diutinum
- Acute hemorrhagic edema of Infancy (AHEI)
- Granuloma faciale
LEUKOCYTOCLASTIC VASCULITIS
POSTCAPILLARY VENULES AND ARTERIOLES

- Secondary causes:
  - Drugs; exogenous antigens
  - Infections (immune complexes)
  - Cryoglobulinemia, probably all types
  - Autoinflammatory syndromes (FMF and others)
  - Hematologic, lymphoreticular and solid tumors
  - Hypereosinophilic syndrome
  - Pustular vasculitis; bowel bypass, inflammatory bowel disease
  - Cystic fibrosis
  - Alpha1 antitrypsin deficiency
  - Others...

PATHOGENESIS

- Humoral Immunity
  - Immune complexes
  - Antineutrophil cytoplasmic antibodies (ANCA)

- Cell Mediated
  - T-lymphocyte response
  - Granuloma formation

The etiopathogenesis of small vessel vasculitis, according to ALL the textbooks, is from deposition of circulating immune complexes that deposit in vessel wall, fix complement and recruit effector neutrophils. There is really very little to support this and it is based on circumstantial data.

IMMUNE COMPLEX THEORY FOR LCV

- Often positive serum tests for CICs
- Immunostaining in damaged vessels for IgG and complement.
- However:
  - Areas of immunostaining without damage frequently seen.
  - Usually no inciting drug or antigen identified.
  - Identical histopathology occurs in vasculitides without postulated immune complex etiology.
  - Are antibodies/complement simply reacting with exposed vascular Ag?
  - No vasculitis is seen in serum sickness, the Godzilla of circulating immune complex disorders.
PATHOGENESIS

- Possibly immune complexes in small vessel vasculitis ???
- Antibody mediated in medium vessel vasculitis with cANCA or pANCA?
- T-cell mediated in vasculitis of larger vessels or with granuloma formation?

ANCA

ANCAs are anti-neutrophil cytoplasmic IgG antibodies. They are targeted to protein determinants within neutrophils and monocytes and seem to be useful markers for several multisystem necrotizing vasculitis syndromes. The ANCA associated vasculitides include Wegener’s granulomatosis, Microscopic polyarteritis and Churg-Strauss syndrome. They are useful in classification and corroboration and may be pathologic. They DO NOT make the diagnosis any more than ANAs do collagen vascular diseases.

ANCA

- Indirect immunofluorescence on alcohol fixed PMNs
- Interpretation is somewhat observer dependent.
- Should be confirmed with Enzyme Immunoassay.
ANCA

- cANCA (cytoplasmic) is a 29kd serine proteinase found in primary (azurophilic) myeloid granules named PROTEINASE 3 (PR3).
- pANCA (perinuclear) is usually a cationic protein, myeloperoxidase (MPO) found in azurophilic granules.
- Atypical ANCAs mimic pANCA pattern, but are of variable nonmyeloperoxidase targets.
- cANCA is same as PR3-ANCA
- pANCA is same as MPO-ANCA

cANCA

- cANCA is highly specific for Wegener’s and Microscopic polyarteritis and only occasionally positive in other diseases.
- Rarely it is seen in drug-induced vasculitis.
- Positive in 40-50% of patients with idiopathic RPGN (a Wegener’s spectrum?)
- cANCA+ diseases have a lytic, necrotizing vascular pathology without immunoreactants.
- They frequently have patchy, segmental vascular involvement.
- cANCA+ diseases frequently have prominent pulmonary injury and renal injury.
- The lung injury may resemble a rapidly progressing pneumonia sometimes with hemorrhage.
- The kidneys show focal and segmental, paucimmune, crescentic rapidly progressive glomerulonephritis.
pANCA

- + in 60% of microscopic polyarteritis (other 40% are cANCA+).
- Usually + in Churg-Strauss syndrome.
- + in some overlap syndromes with features of Churg-Strauss (i.e. asthma, eosinophilia).
- + in 1/3 of patients with idiopathic RPGN felt to be renal limited Microscopic polyarteritis.

THE PATIENT; SIGNS AND SYMPTOMS

- Unexplained constitutional symptoms:
  - Fever
  - Fatigue
  - Weight loss, involuntary
  - Malaise
- Unexplained parameters of inflammation:
  - Elevated ESR, CRP
  - Anemia of chronic disease
  - Thrombocytosis
  - Decreased serum albumin

THE PATIENT; SIGNS AND SYMPTOMS

- Vasculitic skin rash
- Multisystem disease
- Nondestructive arthritis/arthritis
- Polymyalgia rheumatica
- Anytime you consider the diagnosis of:
  - SBE
  - Neoplasia
  - Metastatic malignancy
  - Endemic pneumonia/Infection (TB, Blunt, Bite etc.)
  - FHO
  - Collagen vessel disease
  - Atrial myxoma
  - Cholesterol emboli

THINK OF VASCULITIS!

VASCULITIS; CNS

- Headache
- Neuropsychiatric abnormalities
- Confusion/delirium
- Encephalopathy
- Seizures
- Stroke
- Focal fluctuating cerebral, cerebellar or brain stem abnormalities
- Visual hallucinations
- Psychosis
- Mononeuritis multiplex
- Distal sensorimotor neuropathy
- Multiple mononeuropathies
- Cranial nerve palsy
- Sensorineural hearing loss
VASCULITIS; THE EYE
- Pseudotumor cerebri
- Optic atrophy
- Episcleritis
- Uveitis

VASCULITIS; PULMONARY
- Dyspnea
- Cough
- Hemoptysis
- Pulmonary hemorrhage
- COPD
- Fixed infiltrates of diverse patterns
- Nodules
- Pleural effusions

VASCULITIS; CARDIOVASCULAR
- Pericarditis
- Constrictive pericarditis
- Coronary arteritis
- Myocardial infarction
- Ischemia
- Arrhythmias
- HTN
- EKG changes
- CHF secondary to HTN, ischemia, necrosis
- Restrictive cardiomyopathy

VASCULITIS; GI
- Nausea, vomiting
- Abdominal pain and cramping
- Hematochezia
- Melena
- Diarrhea
- Bowel ischemia, infarction
- Obstruction
- Peritonitis
- Ascites
- Cholecystitis
VASCULITIS; MUSCULOSKELETAL
- Arthritis/arthralgias
- Cramping and muscle pain
- Weakness

VASCULITIS; RENAL
- Proteinuria, hematuria, casts
- Renal insufficiency/failure
- Renal infarcts
- HTN

THE WORK-UP
- HISTORY AND PHYSICAL EXAM
- BIOPSY OF ACCESSIBLE AFFECTED TISSUE
- Laboratory directed biopsy
  - Nerve conduction i.e. sural nerve
  - EMG and muscle biopsy
- Kidney biopsy if active sediment
- Lung biopsy-open preferred
- Blind biopsy of testis or rectum if no other affected tissue available.
- Angiogram, MRA

LABORATORY WORK-UP
- SMA28
- Urinalysis and micro
- 24 hour urinanalysis for total protein, creatinine clearance
- stool guia
- ANCA (MPO and PR3)
- Collagen vascular screen
- Cryoglobulins
- Immune complex studies (Raji cell, RF, C1q)
- Pan-culture
- 2D echocardiogram
- Hepatitis B and C screen
- Tests for monoclonal gammopathies (SPEP, SIEP, immunofixation)
- Radiographic studies; CXR, sinus films, CT scans etc. as indicated.
TREATMENT GENERALITIES
Small vessel vasculitis (LCV, hypersensitivity)

- Skin and arthralgia limited: NSAIDs, colchicine, low to moderate dose oral corticosteroids.
- More severe or unresponsive; initial high dose steroids with gradual taper (per disease activity).
- More severe and unresponsive; high dose steroid and immunosuppressive drugs such as azathioprine, mycophenolate mofetil, methotrexate etc.

For ANCA+ small and medium vessel vasculitis:
- Initial induction with high dose steroids (p.o. vs. IV pulse) and moderate or high dose cyclophosphamide (usually p.o.) or rituximab.
- Steroid tapering over 6-9 months
- Cyclophosphamide for 3-6 months
- Then, maintenance with azathioprine or methotrexate +/− chronic steroids.
- For nonsevere disease daily prednisone and weekly methotrexate.

TREATMENT CONTROVERSIES FOR ANCA POSITIVE VASCULITIS

- Pulse vs continuous cyclophosphamide
- Rituximab vs cyclophosphamide
- Mycophenolate mofetil
- Immunoadsorption or lymphocytapheresis
- Plasma exchange as an adjunctive therapy
- IVIG for refractory disease

CONTROVERSIES IN MAINTENANCE OF ANCA POSITIVE VASCULITIS

- Azathioprine vs cyclophosphamide
- Azathioprine vs mycophenolate mofetil
- Azathioprine vs methotrexate
- Leflunomide vs methotrexate
- Etanercept as an adjunctive therapy
- Co-trimoxazole to prevent relapses
TREATMENT GENERALITIES

- For all patients on anticipated chronic immunosuppression-screen for TB, hepatitis B and C, HIV before starting therapy.
- For all patients on chronic steroids-baseline and periodic DEXA and daily VitD3 and calcium. Therapy if osteopenic or osteoporotic.
- Prophylactic antibiotics (e.g. Bactrim) to prevent relapses/flares and secondary *Pneumocystis* infection.