Vasculitides and Vaso-Occlusive Disease

Oakwood Southshore Medical Center/Beaumont Health Dermatology Residency Program

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Overview

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  - Urticarial vasculitis
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  - Granuloma faciale
  - Cryoglobulinemia
  - Churg-Strauss
  - Wegener’s
  - PAN

- Vaso-Occlusive Disease
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  - Calciphylaxis
  - Cholesterol emboli
  - Antiphospholipid syndrome
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Malignant atrophic papulosis
Vasculitides

- The classification and cutaneous signs of vasculitis are a reflection of the size of vessels involved
  - Small vessel
  - Small to medium vessel “mixed”
  - Medium vessel
  - Large vessel
Cutaneous Small Vessel Vasculitis
Leukocytoclastic Vasculitis (LCV)

- General term describing the histopathologic features of LCV involving only small cutaneous blood vessels (post-capillary venules of the dermis), irrespective of the etiology
- Initiated by the deposition of circulating immune complexes within and around vessel walls
LCV

• Etiology
  – Idiopathic (50%)
  – Post Infectious (15-20%)
  – Underlying Connective Tissue Diseases (15-20%)
  – Drug Induced (10-15%)
  – Hematologic or Solid Organ malignancies (2-5%)
LCV

• Clinically presents as **palpable purpura**, with erythematous macules, papules, and vescicles over the lower extremities and other dependent areas.

• Prognosis depends on the severity of systemic involvement.
LCV

• Pathology
  – Perivascular and interstitial infiltrate of neutrophils with nuclear dust (leukocytoclasia)
  – Fibrin within the vessel wall and extravasation of erythrocytes
LCV

• **Treatment**
  – **Rule out systemic vasculitis**
  – Remove any suspected triggers
  – Supportive care for skin-limited disease (90% spontaneous resolution)
  – Chronic (>4 weeks)
    • Colchicine and dapsone may be useful for skin and joint disease
    • 1mg/kg/day prednisone for severe or progressive disease
Urticarial Vasculitis

• Synopsis:
  – Condition that **clinically resembles urticaria** but also demonstrates features of LCV histologically

Epidemiology:
  – Peak incidence is in the fifth decade with a predilection for females
  – Two Forms
    • Normocomplementemic (70-80%): benign course, ~3 year duration
    • Hypocomplementemic (~25%): almost exclusively in women
      – ↓ complement, anti-C1q antibody
Urticarial Vasculitis

• Pathogenesis:
  – Complement activation triggers mast cell release of inflammatory mediators, such as TNF-α

• Associated with:
  – Sjögren’s syndrome, SLE, serum sickness, cryoglobulinemia, infections, medications, and hematologic malignancies
Clinically: Urticarial papules and plaques with associated burning or pain, lasting >24 hours.

Pathology: Prominent edema in upper dermis; mild infiltrate; similar to LCV.
Urticarial Vasculitis

• Treatment
  – Workup for any associated systemic disease
  – Antihistamines may reduce swelling and pain of cutaneous lesions
  – Oral corticosteroids, NSAIDs, Colchicine, Dapsone, Antimalarials
Henoch-Schönlein Purpura (HSP)

• **Synopsis**
  - Specific type of cutaneous small vessel vasculitis (CSVV) with **vascular IgA deposition** that typically affects children (M>F) after a respiratory tract infection

• **Pathogenesis**
  - HSP frequently presents 1 to 2 weeks following a URI, especially in children
  - Associated with positive antistreptolysin O titers, but no causal role has been demonstrated
  - IgA deposits in the postcapillary venules of the skin and mesangium
  - Circulating IgA-containing immune complexes with increased serum levels of IgA
HSP

• Clinical Presentation:
  – Erythematous macules or urticarial papules that evolve into palpable purpura with a predilection for the lower extremities and buttocks.
  – Classic “tetrad”: palpable purpura, arthritis, abdominal pain, and hematuria.

• Pathology:
  – Leukocytoclastic vasculitis of the small dermal blood vessels
  – DIF demonstrates perivascular IgA, C3 and fibrin deposits.

HSP

• Indistinguishable from LCV histologically

• DIF = perivascular IgA

• Treatment:
  – HSP is commonly self-limited, resolving over the course of weeks to months
  – Don’t forget UA to evaluate renal involvement!

Erythema Elevatum Diutinum (EED)

• **Synopsis:**
  – Rare chronic dermatosis, favoring the extensor surfaces, usually found in middle-aged and older adults

• **Pathogenesis:**
  – Due to circulating immune complexes, with repeated deposition, associated inflammation and partial healing
  – **Associations**
    • Autoimmune diseases, infections, inflammatory bowel disease, and hematologic disorders
EED

• Clinical Presentation:
  – Violaceous, red–brown or yellowish papules, plaques or nodules that are symmetrically distributed
  – Favor acral and periarticular sites, specifically the extensor surfaces of the elbows, knees, ankles, hands and fingers

Early lesion: LCV with neutrophilic infiltrate

Late Lesion: marked perivascular fibrous thickening

• **Treatment**
  – **Dapsone** shows excellent improvement, however, relapses are common
Granuloma Faciale

• Synopsis:
  – An idiopathic cutaneous disorder, characterized by red–brown plaques on the face, which occurs predominately in middle-aged white males

• Pathogenesis:
  – A role for interferon-γ as an important proinflammatory mediator in this disorder has been suggested, as has elevated local IL-5 production
Granuloma Faciale

• Clinical Presentation:
  – Presents as a solitary, asymptomatic, smooth red–brown to violaceous plaque on the face
  – Very rare to have extra-facial sites of involvement

Granuloma Faciale

- Pathology
  - LCV
  - Normal epidermis, **grenz zone** above diffuse infiltrate of neutrophils, histiocytes, and lymphocytes
  - Often hemosiderin deposition within the dermis

- Treatment
  - Often resistant to treatment
  - IL/topical corticosteroids, **dapsone**, clofazamine, topical tacrolimus
  - Excision, cryosurgery, dermabrasion, electrosurgery, CO2 or pulsed dye lasers

Mixed Vessel Vasculitis
Cryoglobulinemia

- **Synopsis:**
  - Cold-precipitable immunoglobulins (single or mixed), divided into three types

<table>
<thead>
<tr>
<th>Type</th>
<th>Molecular Composition</th>
<th>Associations</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Monoclonal IgM &gt; IgG</td>
<td>Plasma cell dyscrasias, Lymphoproliferative disorders (LPD)</td>
<td>Raynaud’s phenomenon, retiform purpura, gangrene, acrocyanosis, arterial thrombosis</td>
</tr>
<tr>
<td>II (Mixed)</td>
<td>Monoclonal IgM (or IgG) with polyclonal IgG</td>
<td>HCV, HIV, autoimmune connective tissue diseases, LPD</td>
<td>Vasculitis with palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis</td>
</tr>
<tr>
<td>III (Mixed)</td>
<td>Polyclonal IgM complexed with polyclonal IgG</td>
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Cryoglobulinemia

- **Pathogenesis:**
  - Cryoglobulinemic vasculitis occurs when immune complexes form from circulating cryoglobulins and then deposit within the walls of small vessels

- **Treatment**
  - Treat the underlying cause (ex: HCV: IFNα + ribavarin)
Churg-Strauss Syndrome

• Synopsis:
  – ANCA associated, granulomatous, necrotizing vasculitis of small vessels, that affects multiple organ systems. Distinguished by asthma and eosinophilia

• Pathogenesis:
  – Triggering factors for the onset of symptoms include, vaccination, desensitization therapy, leukotriene inhibitors and rapid discontinuation of corticosteroids
  – T lymphocytes, eosinophils and ANCA all play a role
  – Th2 cells are implicated in granuloma formation
Churg-Strauss Syndrome

• Clinical Presentation:
  – Palpable purpura (typically lower lower extremities), SubQ nodules (scalp or extremities), urticaria, and livedo reticularis
  – Labs: ↑IgE, **p-ANCA** (anti-myeloperoxidase {MPO})

• Treatment
  – Oral corticosteroids +/- cytotoxic agents
Granulomatosis with Polyangitis (Wegener’s)

• Synopsis
  – **Triad** of granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing small vessel vasculitis, and pauci-immune **glomerulonephritis**

• Pathogenesis
  – Th1 mediated granuloma formation, and small-medium vessel vasculitis.

• Clinically
  – May present with mucocutaneous findings including palpable purpura, oral ulcers, red friable gingiva, painful ulcers or nodules (mimicking pyoderma gangrenosum).
  – Labs: ↑ESR, WBC, **c-ANCA** (anti-proteinase-3 {PR-3})
Granulomatosis with Polyangitis

• Treatment
  – Systemic corticosteroids in conjunction with oral cyclophosphamide

Medium Vessel Vasculitis
Polyarteritis Nodosa (PAN)

• Synopsis:
  – A multisystem vasculitis characterized by segmental necrotizing vasculitis that involves predominantly medium sized blood vessels.
    • Cutaneous PAN: skin limited variant, usually benign but chronic (10% of all cases)

• Pathogenesis
  – Associated with infections, inflammatory diseases, malignancies (especially hairy cell leukemia), and medications.
    • IBD, SLE, HBV, & strep
PAN

• Clinically
  – Palpable purpura, livedo reticularis, retiform purpura, “punched out” ulcers, SubQ nodules, acral gangrene

• Treatment
  – Classic PAN: systemic corticosteroids
  – **Cutaneous PAN**: topical or intralesional steroids, occasionally oral

Diagnostic Approach to Vasculitis

• History and Physical
  – Antecedent illnesses or exposures
  – Autoimmune connective tissue disease or malignancy
  – Systemic symptoms in ROS
  – Complete head and neck, cardiopulmonary, abdominal, musculoskeletal and neurologic examination should be performed
Diagnostic Approach to Vasculitis

- **Histological Examination:**
  - Tissue biopsy from affected areas for possible diagnosis
  - H/E and DIF samples

- **Laboratory Examination:**
  - CBC with Diff, LFT, BUN/Cr
  - ANCA, Cryoglobulin, Complement levels, RF, HBV/HCV serologies
  - ANA if signs of CTD
  - Urine dipstick and microscopy, stool guaiac
  - Consider blood cultures, imaging as indicated
Treatment

- Rule out any obvious infection, inflammatory, or neoplastic etiology
  - A treatable etiology exists in 50%
- **Systemic disease should always be ruled out**, or followed up as appropriate
- Treatment as appropriate for type of vasculitis
Vaso-Occlusive Diseases
Vaso-Occlusive Disease

- The differential diagnosis can be extensive and the evaluation can be trying
- Distinguish between inflammatory versus non-inflammatory
- Telltale finding of retiform purpura, macular, violaceous, connecting rings that form a netlike pattern
- Accurate diagnosis is critical to appropriate therapy, as treatment for inflammatory disease is vastly different than occlusive diseases
Heparin Necrosis

Synopsis:
- Iatrogenic syndrome causing necrosis 5-10 days after exposure to SubQ or IV heparin
- Heparin necrosis can happen with low molecular weight heparin (lower risk) or unfractionated heparin

Epidemiology:
- Heparin-induced thrombocytopenia (HIT) occurs in 1-5% of adults; thrombosis percentages range from 30 - 90% of patients

Pathogenesis:
- Secondary to antibody binding of heparin plus platelet factor 4 complexes
- Leads to platelet aggregation & consumption
Heparin Necrosis

- Clinical:
  - Lesions are tender, non-inflammatory, purpuric/necrotic with a retiform morphology at or distant to the site of administration

Heparin Necrosis

• Pathology:
  – Pathology often shows non-inflammatory occlusion of vessels involving either the microvasculature, arterial, or venous system
  – **Platelet plugs are “white”** vs usual “red” clot of fibrin thrombi
Heparin Necrosis

• Treatment:
  – Discontinue heparin
  – Argatroban, danaparoid, or lepirudin
  – Do not begin warfarin in this setting as initial decrease in protein C may cause further thrombosis or necrosis
Warfarin Necrosis

• Epidemiology:
  - Relatively rare
  - 4x more common in women, specifically in 70s-80s

• Pathogenesis:
  - Necrosis occurs within 2-5 days of starting therapy (> w/loading dose)
  - Vitamin K sensitive factors include II, VII, IX, X, protein C (VII and protein C shortest half life)
  - Occurs more commonly in patients with inherited defects in protein C
Warfarin Necrosis

• Clinical:
  – Prefers fatty areas of the body (butt, hip, thigh, breast).
  – Presents with pain —> erythema —> hemorrhage and necrosis
Warfarin Necrosis

- **Pathology:**
  - Fibrin-platelet thrombi are present in venules and arterioles in the deep dermis and subcutis

- **Treatment:**
  - Discontinue warfarin, administer vitamin K and heparin

Calciphylaxis

Synopsis:
- Progressive vascular calcification and ischemic necrosis of the skin and soft tissues

Epidemiology:
- Female predominance
- Associated with diabetes mellitus, obesity, and poor nutritional status

Pathogenesis:
- Protein C dysfunctional in some patients
- End-stage renal failure common, but may be associated with primary hyperparathyroidism
- No known trigger in some instances
- Mortality is HIGH (~85%) with proximal involvement having worse prognosis
Calciphylaxis

Pathology: intravascular calcium deposits, chiefly within small and medium-sized venules and arterioles

Calciphylaxis

- Clinical:
  - Lesions present as painful, violaceous, reticulated patches with the progression to bullae; gray color signifies impending tissue necrosis

Calciphylaxis

• Treatment
  – Normalizing calcium-phosphate product (medication and low phosphate diet vs parathyroidectomy)
  – Restoring tissue perfusion and good wound care
  – Other proposed treatment modalities include sodium thiosulfate, pamidronate, cinacalcet, hyperbaric oxygen, and low dose tissue plasminogen activator
Cholesterol Emboli

• Synopsis:
  - Fragmentation of ulcerated atheromatous plaques
  - Three settings that prompt embolization: arterial or coronary catheterization (emboli within hours-days), prolonged anticoagulation (1-2 months after therapy), acute thrombolytic therapy (hours to days)

• Epidemiology:
  - Men 50 years of age or older
Cholesterol Emboli

- **Clinical:**
  - Fever, weight loss, altered mental status, new-onset hypertension
  - Cutaneous manifestations, (most to least common): livedo reticularis, peripheral gangrene, cyanosis, ulceration, nodules, and purpura
  - Laboratory values: peripheral eosinophilia; decreased complement; leukocytosis; pyuria; increased ESR, BUN, and serum creatinine

Cholesterol Emboli

- Pathology:
  - Elongated clefts within small vessels and thrombi, usually at dermal-subcutaneous junction
  - Frozen section demonstrates doubly refractile crystals
    (Biopsy specimens should be an elliptical incision and include subcutaneous fat)

Antiphospholipid Syndrome

• **Synopsis:**
  - Characterized by the presence of autoantibodies directed against phospholipids
  - Associated with repeated episodes of thrombosis, fetal loss, and thrombocytopenia

• **Epidemiology:**
  - Female predominance and common in 3\textsuperscript{rd} to 5\textsuperscript{th} decade
Antiphospholipid Syndrome

• Clinical:
  - Livedo reticularis +/- retiform purpura, leg ulcers, pseudovasculitis, digital gangrene, cutaneous necrosis, splinter hemorrhage

  - Most common extracutaneous findings are DVT/PE and CNS disease
Antiphospholipid Syndrome

Clinical Criteria:
• Vascular thrombosis
  – One or more clinical episodes of arterial, venous or small vessel thrombosis

• Complications of pregnancy
  – One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of pregnancy; or
  – One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or
  – Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Antiphospholipid Syndrome

Laboratory Criteria:

• Anticardiolipin antibodies*, IgG or IgM, present at moderate or high levels† on two or more occasions at least 12 weeks apart
• Lupus anticoagulant antibodies on two or more occasions at least 12 weeks apart
• Anti-β2-glycoprotein I antibodies, IgG or IgM (in titer >99th percentile) on two or more occasions at least 12 weeks apart

*β2-glycoprotein I-dependent.
†Several thresholds exist for low versus moderate-to-high: (1) >40 international “phospholipid” units; (2) 2–2.5× the median level of anticardiolipin antibodies (ACA)
Antiphospholipid Syndrome

- Treatment:
  - Initially heparin, followed by long term warfarin therapy
  - Target INR 2-3
Sneddon Syndrome

• **Synopsis:**
  - AKA: *idiopathic livedo reticularis with cerebrovascular accidents*

• **Pathogenesis:**
  - Persistent livedo reticularis associated with systemic arterial thrombi, labile hypertension, and recurrent neurologic symptoms
  - May appear as a manifestation of antiphospholipid syndrome or may represent a distinctive vasculopathy affecting smaller arteries and larger arterioles, especially in the skin and the brain
Sneddon Syndrome

• Epidemiology:
  - Most commonly affects young women
  - Onset in 3rd to 4th decade of life
  - Mortality rate of ~10%
Sneddon Syndrome

- Clinical:
  - Persistent and widespread livedo reticularis which may precede the onset of neurologic disease by several years
  - CNS disease usually presents as TIAs, stroke, or dementia
  - Patient may have a history of fetal loss

Sneddon Syndrome

- Pathology:
  - Endothelial inflammation, followed by subendothelial myointimal hyperplasia, with partial and complete occlusion of the involved arterioles
  - **White areas, rather than red areas should be biopsied (center of livedo)**
  - 4mm punch biopsy has 27% sensitivity, but increases to 80% if three biopsies are performed

Sneddon Syndrome

- Treatment:
  - Warfarin, however may not be completely effective
  - If patient has antiphospholipid antibodies a target INR of 2-3 should be achieved
  - Corticosteroids and immunosuppressive agents do not prevent cerebrovascular disease
Livedoid Vasculopathy
(Atrophie Blanche)

• Synopsis:
  - Chronic cutaneous disease favoring distal lower extremities, predominantly in females

• Pathogenesis:
  - May be primary (idiopathic) or secondary to chronic venous hypertension, varicosities, or hypercoagulable states (eg. APLS)
  - Occlusion of small dermal vessels by fibrin thrombi is a primary event
Livedoid Vasculopathy
(Atrophie Blanche)

• **Clinical:**
  - Painful punched out ulcers on a background of livedo reticularis
  - Ulcers may heal as stellate atrophic hypopigmented scars with peripheral telangiectasia

Livedoid Vasculopathy
(Atrophie Blanche)

• Pathology:
  - Atrophic or ulcerated epidermis
  - Thrombi in dermal vessels surrounded by hyalinization of walls
  - Dermal fibrosis and extravasated RBC

Livedoid Vasculopathy
(Atrophie Blanche)

• Treatment
  – No treatment consistently effective
  – Smoking cessation
  – Antiplatelet agents: low dose aspirin, dipyrimadole, pentoxyfyline
  – Anticoagulants: warfarin (depending on underlying etiology)
  – Other clinical scenarios may support the use of anabolic steroids, hydroxychloroquine, folic acid
Malignant Atrophic Papulosis
(Degos Disease)

• Synopsis:
  - Rare, often fatal, multisystem vaso-occlusive disorder

• Pathogenesis:
  - Unknown but assumed to be a vasculopathy
Malignant Atrophic Papulosis
(Degos Disease)

• Epidemiology:
  - Occurs between the 2\textsuperscript{nd} to 4\textsuperscript{th} decade of life
  - Women and men affected equally

• Clinical:
  - Cutaneous features precede systemic features
    • Crops of small 2-5mm erythematous papules on trunk or extremities
    • Papules evolve over 2-4 weeks developing a central depression, ending in an atrophic scar with surrounding telangiectasia
Malignant Atrophic Papulosis
(Degos Disease)

- Clinical cont:
  - Systemic symptoms can include CNS lesions leading to cerebrovascular accidents
  - Infarctive GI lesions may lead to bowel perforation
Malignant Atrophic Papulosis  
(Degos Disease)

- **Pathology**
  - Epidermal atrophy with overlying hyperkeratosis
  - Underlying wedge shaped area of ischemia extending to the deep dermis
  - Acid mucopolysaccharides are present in abundance in the dermis
  - Late stages resemble lichen sclerosis et atrophicus

Malignant Atrophic Papulosis
(Degos Disease)

• Treatment
  – No consistently proven treatment
  – Aspirin +/- pentoxifylline
  – IVIg
Thank you!

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