A Short Review of Cutaneous Vasculitis

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Introduction

- The vasculopathic reaction pattern is an extensive ‘catch all’ comprising vasculopathies as well as acute leukocytoclastic vasculitis, neutrophilic dermatoses, chronic lymphocytic vasculitis and granulomatous vasculitis
- Key feature of many systemic diseases that involve the skin

Introduction

- Diseases of cutaneous vessels important cause of morbidity, and sometimes mortality
- Basis for extensive multidisciplinary collaboration among rheumatologists, dermatologists, and dermatopathologists

Introduction

- Morphologic groups include:
  - Non inflammatory purpuras: extravasation of erythrocytes without inflammation or occlusion, i.e., senile purpura
  - Vascularoly: Vascular occlusion with associated downstream changes, i.e., skin ulceration and localized necrosis

Introduction

- Urticaria: Immunity changes leads to vascular changes, leakage of intravascular contents into dermis (can overlap with acute vasculitis)
- Acute vasculitis: True inflammation of vessel walls, with fibrinoid necrosis, infiltration by neutrophils, and leukocytoclasis (neutrophilic debris)
- Non neutrophilic vasculitis: Inflammation of vessel walls, but driven by either lymphocytes or histiocytes with formation of granulomatous changes
- Neutrophilic dermatoses (i.e., Sweet syndrome): Dermal infiltration by neutrophils but acute vasculitis is secondary, not primary
Case 1

16 year old female with erythematous papules and nodules on her lower extremities. The biopsy is from a nodule on the left lower leg.

Question 1: What is the best diagnosis for this lesion?

- A. Lupus panniculitis
- B. Polyarteritis nodosa
- C. Subcutaneous panniculitis like T cell lymphoma
- D. Lipodermatosclerosis
- E. Subcutaneous granuloma annulare
Polyarteritis nodosa

- Inflammation of small and medium sized muscular arteries
- Involves visceral organs like kidneys, liver, gastrointestinal tract and nervous system
- Constitutional symptoms are present, including fever, weight loss, fatigue, arthralgia, myalgia
- 5 year survival=50%

Polyarteritis nodosa

- Can have a cutaneous only version
- Patients present with nodules, livedo reticularis, and/or ulceration involving the lower limbs (palpable purpura)
- Mild constitutional symptoms such as fever can be present
- Prognosis is very good, but recurrent and chronic course

Polyarteritis nodosa

- Many causes documented, including formation of immune complexes, angiogenic cytokines, hepatitis B and C, and preceding bacterial infections
- Treatment includes corticosteroids under occlusion for cutaneous lesions, oral corticosteroids, and non steroidal anti inflammatory agents such as mycophenolate mofetil

Polyarteritis nodosa

- Superficial biopsies may show no findings, so a deep incisional biopsy is recommended
- If an ulcer is present, take a biopsy from near the center of the ulcer, as the affected artery may be directly underneath
- Acute inflammation of small and medium sized arteries

Polyarteritis nodosa

- Fibrinoid necrosis of vessel walls, fibrin thrombi formation, and infusion of walls with acute inflammatory cells
- Leukocytoclasis can be present
- Partial to full involvement of the vessel may be seen
- Some vessels may be uninvolved

Polyarteritis nodosa

- Can see vessels at all stages of involvement/development (none to partial to full; early and late lesions)
- Can see deposition of IgM and sometimes C3 in vessel walls on direct immunofluorescence
- Older lesions show intimal thickening and luminal obliteration with an accompanying mononuclear infiltrate
Question 2: What is an important histologic differential diagnostic consideration?

• A. Necrobiosis lipoidica diabeticorum
• B. Nodular vasculitis
• C. Pancreatic panniculitis
• D. Lupus panniculitis
• E. NK/T cell lymphoma

Nodular vasculitis

• Erythema induratum-nodular vasculitis thought to be the same entity, presumably related to tuberculosis, regardless of whether organisms are obtained from lesions via cultures or PCR methodology
• Characterized by recurrent crops of tender erythematous nodules, predilection for calves

Nodular vasculitis

• Inflammatory changes within subcutis predominantly
• Diffuse lobular panniculitis, with granulomatous inflammation, focal necrosis, and vasculitis
• Granulomas are poorly formed, and accompanied by mixed inflammation

Nodular vasculitis

• Vasculitis involves all sizes of arteries and veins (separating this entity from both thrombophlebitis and polyarteritis nodosa)
• In nodular vasculitis, vasculitis and inflammatory changes involves contiguous lobules (diffuse), whereas in polyarteritis nodosa, inflammatory changes limited to the vicinity of the involved vessel (localized)

Case 2

55 year old woman with multiple new lesions which the patient thought were spider bites.
Question 3. What is the best diagnosis for this entity?

- A. Lichen planus
- B. Dermatitis herpetiformis
- C. Degos’ disease
- D. Mucha Habermann syndrome
- E. Squamous cell carcinoma in situ

Malignant atrophic papulosis (Degos’ disease)

- Rare multisystem vaso-occlusive disease
- Associated with infarctive lesions of visceral sites, particularly GI tract
- Crops of papules develop, evolve slowly to become umbilicated with a porcelain center and telangiectatic rim
- Finally, lesions resolve with an atrophic scar
Malignant atrophic papulosis (Degos’ disease)

- There are cutaneous lesions-only versions which have a benign course
- Histology: epidermal atrophy with overlying hyperkeratosis and wedge shaped area of cutaneous ischemia
- Dense lymphocytic infiltrate
- Overlap histologically with lichen sclerosus or early morphea

Endothelial swelling is seen of venules and to a lesser extent, arterioles
- Extensive deposition of mucopolysaccharides in the dermis, thought to be a secondary event

Question 4: The patient was found to have several year history of abdominal pain and bleeding. Her follow up was set up with various specialists. Who should follow this patient?

- A. Podiatrist
- B. Endocrinologist
- C. Neurologist/neurosurgeon
- D. Allergist
- E. Oncologist

Patient should be followed by neurologist or neurosurgeon for CNS events

- Degos disease is thought to be a multi system vaso occlusive phenomenon
- CNS events is a potential avenue of fatality

Case 3

54 year old man with 2 episodes of 3rd/4th right toe swelling, pruritus, and erythema.
Question 5: What is the best diagnosis for this lesion?

- A. Lymphoma
- B. Pernio
- C. Bullous pemphigoid
- D. Syphilis
- E. Polymorphous light eruption

Perniosis

- Localized inflammatory lesion which individuals experience secondary to cold weather
- **Classic perniosis** (chilblains): fingers, toes, sometimes ears
- **Chilblain lupus**: lesions occurring in the setting of lupus erythematosus that mimic pernio
- Equestrian perniosis: occurs on thighs and buttocks of female equestrians in winter

Perniosis

- On histopathology, perniosis is considered a “lymphocytic” vasculitis
- Superficial and deep perivascular infiltrates of lymphocytes are seen as well as perieccrine inflammation
- Intramural inflammation and vessel wall thickening can be seen as well
Perniosis
- There can be subepidermal edema but this may not be fully formed
- Interface activity and dermal mucin deposition may accompany lesions of lupus erythematosus, and may be very extensive (more than cold related pernio)

Perniosis
- A leukocytoclastic vasculitis is almost never seen
- Lack of subepidermal edema and deep infiltrate does not exclude this diagnosis: may depend on when along the disease process the biopsy was taken
- If lupus is suspected, further work up is indicated

Question 6: Recently a study examined the expression of which marker in large atypical cells of pernio?
- A. CK5/6
- B. PDL-1
- C. Sox10
- D. STAT-6
- E. CD30

CD30 expression in large atypical lymphocytes
- A recent study from the Univ of Pennsylvania examined expression of CD30 in the large atypical cells of pernio
- Activated T cells that express CD30 can be a part of any inflammatory infiltrate and do not necessarily constitute a diagnosis of lymphoma

Case 4
27 year old woman with right upper cheek lesion.
Question 7: What is the best diagnosis for this lesion?

- A. Granuloma faciale
- B. Eosinophilic fasciitis
- C. Arthropod bite reaction
- D. Lymphomatoid papulosis
- E. Mast cell disease

Granuloma faciale

- Rare dermatosis manifesting as one or more brown red plaques or nodules
- Face, solitary
- Middle aged males
- Persistent, asymptomatic
- Thought to be a vasculitis
Granuloma faciale

- Dense polymorphous inflammatory infiltrate involving the reticular dermis
- Grenz zone
- Can extend to subcutis
- Eosinophils, neutrophils, lymphocytes and histiocytes
- Endothelial swelling with perivascular deposition of fibrinoid material (toxic hyalin)

Question 8: Granuloma faciale is thought to be related to which entity?

- A. Squamous cell carcinoma
- B. Mycosis fungoides
- C. Urticarial vasculitis
- D. Erythema elevatum diutinum
- E. Pityriasis rubra pilaris

Erythema elevatum diutinum

- EED has many histologic similarities to GF but neutrophils tend to predominate over eosinophils
- No defined Grenz zone
- Toxic hyalin more well developed
- Clinical scenario very different– EED is acrally and symmetrically distributed whereas GF is primarily on the face

Case 5

52-year-old male with infectious process on the glans penis, now with 6 mm pustule with surrounding hyperpigmentation on the left foot. The clinical differential includes infectious vs. pustular arthropod vs. bullous disorder.
Question 9: What is the best diagnosis for these findings?

- A. Polyarteritis nodosa
- B. Vasculopathy
- C. Lupus
- D. Toxic epidermal necrolysis
- E. Impetigo

Vascular occlusive diseases (vasculopathy)

- Complete or partial occlusion of vessels fibrin platelet thrombi, but also platelet rich thrombi (TTP), cryoglobulins, cholesterol plugs (atheromas), and fungi (Mucor)
- Clinically, can cause purpura, livedo reticularis, erythromelalgia, ulceration or infarction

Vasculopathy

- Livedo reticularis=netlike pattern of interconnecting macular violaceous rings
- Primary livedo: increased visibility of venous plexus due to cold (most common cause of livedo)
- Secondary livedo: due to vasoocclusive disease

Vasculopathy

- Protein C/S deficiencies
- Prothrombin gene mutations
- Warfarin necrosis
- Disseminated intravascular coagulation
- Purpura fulminans

- Cryoglobulinemia
- Cholesterol/other emboli (infection for example)
- Antiphospholipid syndrome
- Factor V Leiden
- Thrombotic thrombocytopenic purpura

Vasculopathy

- Protein C is a vitamin K dependent plasma glycoprotein which has important anticoagulation activities
- Homozygous deficiency=purpura fulminans as a child
- Heterozygous deficiency=venous thrombosis as an adult
Vasculopathy

- Can have acquired deficiencies as well, due to ulcerative colitis, infection, and anticoagulant therapy
- Protein S is a related vitamin K dependent protein that is a cofactor for activated protein C
- Deficiencies in protein S leads to same presentations as those of protein C

Vasculopathy

- Disseminated intravascular coagulation=acquired disorder
- Activation of coagulation pathway results in thrombi formation in many organ microvasculatures
- Platelets and fibrin are consumed and lead to a hemorrhagic manifestation as well

Vasculopathy

- Purpura fulminans: the skin manifestations of DIC
- Large cutaneous ecchymoses and hemorrhagic necrosis of the skin
- Majority are in infants and children, due to infection or severe protein C/S deficiency
- Erythematous macules that progress to central purpura

Vasculopathy

- Cryoglobulinemia: immunoglobulins which precipitate from serum or plasma upon cooling
- Monoclonal (type I) and mixed (type II, type III)
- Type I=cryoglobulins can be seen in biopsies as intravascular deposits
- Type II, type III=vasculitis

Vasculopathy

- Cholesterol/other emboli=can also include exogenous material or parts of tumor
- Atheromatous plaques often the source, particularly abdominal aorta
- Found often on lower legs, and include livedo reticularis, gangrene, ulceration, cyanosis, purpura
- High mortality

Question 10: A key finding on histology of vasculopathy includes:

- A. Fibrin thrombi
- B. Leukocytoclasis
- C. Panniculitis
- D. Interface dermatitis
- E. Calcification
Vasculopathy: Histology

• On histology, fibrin or fibrin-platelet thrombi may be present in arterioles and/or venules in deep dermis and subcutis
• Surrounding hemorrhage may be present
• Small capillaries and arteries in the superficial dermis may also be involved

Vasculopathy: Histology

• There is overlying wedge shaped necrosis
• If fibrin or fibrin-platelet thrombi, the thrombi may be PAS positive
• Vasculitis is not usually seen (except in type II/type III cryoglobulinemia)

Vasculopathy: Histology

• In infectious septic emboli, organisms can be found in emboli via special stains
• Cholesterol and other emboli: need multiple sections to find cholesterol crystals in arterioles in lower dermis

Case 6

67 year old woman with diagnosis of rule out polyarteritis nodosa.
**Question 11: What is the best diagnosis for these findings?**

A. Polyarteritis nodosa  
B. Wegener’s granulomatosis  
C. Lethal midline granuloma  
D. Allergic granulomatosis (Churg Strauss granuloma)  
E. Erythema annulare centrifugum

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**Churg Strauss Syndrome**

- First described in 1951  
- Syndrome of asthma, fever, peripheral eosinophilia  
- Can have/lead to cardiac failure, renal damage and peripheral neuropathy  
- Tissue diagnosis: tissue eosinophilia, necrotizing granulomatous vasculitis, extravascular granulomas

**Churg Strauss Syndrome**

- Distinguished from classic polyarteritis nodosa and classic Wegener’s granulomatosis (granulomatosis with polyangiitis, GPA)  
- Now called eosinophilic granulomatosis with polyangiitis (EGPA)

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**Churg Strauss Syndrome (EGPA)**

- ANCA positive entity, along with GPA and MPA (microscopic polyangiitis)  
- Classically thought of as Th2 mediated disease  
- Can be limited in involvement and in these cases, diagnosis made on histology (these situations are rare)

**Churg Strauss Syndrome (EGPA)**

- ACR (American College of Rheumatology) criteria:  
  - Asthma  
  - Eosinophilia greater than 10%  
  - Neuropathy  
  - Extravascular eosinophils on biopsy  
  - Paranasal sinus abnormalities  
  - Nonfixed lung infiltrates
Churg Strauss Syndrome (EGPA)

- ANCA-subsets
  - Positive in only 38% of cases
  - Tend to have glomerulonephritis, peripheral neuropathy and purpura
  - ANCA negative: endomyocardial and lung involvement more prevalent

Question 12: The entity with nearly identical clinical and histologic features is:

- A. Acute generalized exanthematous pustulosis
- B. Kawasaki syndrome
- C. Pityriasis lichenoides
- D. Hypereosinophilic syndrome
- E. Sarcoidosis

Churg Strauss Syndrome (EGPA)

- Major differential diagnosis: Hypereosinophilic syndrome
  - Persistent pronounced peripheral eosinophilia (greater than 1550/μL)
  - Organ involvement
  - Absence of a reactive component (i.e., infection, drug, allergy, autoimmune, immune mediated disease)

Hypereosinophilic syndrome (HES)

- Pathogenesis driven classification
  - Myeloid/lymphoid neoplasms with abnormalities in PDGFRα, PDGFRβ, or FGFR1
  - Chronic eosinophilic leukemia
  - Lymphocytic variant that can progress to a leukemia
  - Idiopathic

Hypereosinophilic syndrome (HES)

- Cardiac and pulmonary manifestations can be similar in EGPA and HES, particularly idiopathic HES
- Idiopathic HES will not usually have asthma, sinusitis, or purpura
- Tissue biopsies do not show vasculitis in idiopathic HES but will show eosinophilia
- ANCA negative in idiopathic HES

Hypereosinophilic syndrome (HES)

- ANCA negative EGPA vs HES: very difficult!
- Important because of the neoplastic component of HES (warrants long term follow up)
Hypereosinophilic syndrome (HES)

- Eotaxin-3 (eosinophil-attracting chemokine)
- Serum levels significantly increased in EGPA vs other eosinophil rich DDX considerations like HES
- Cut off level of 80 pg/mL had 87% sensitivity, 99% specificity for EGPA over HES

Case 7

49 year old male with psoriasis who developed pain and swelling of the right ear helix 3 months ago. Erythematosus scaly edematous plaque on helix.
Question 13: What is the best diagnosis for this entity?

- A. Chondrodermatitis nodularis helicis
- B. Relapsing polychondritis
- C. Lupus erythematosus
- D. Infection
- E. Cutaneous mucinosis

Relapsing polychondritis

- Rare multisystem disease manifesting as recurrent inflammatory events attacking cartilagenous organs
- Ears, nose, and tracheobronchial areas particularly affected
- Tenderness and reading of one or both ears common presentation
- Polyarthritis, cardiac lesions, ocular inflammation, and vasculitis

Relapsing polychondritis

- Associated with psoriasis and Behcet’s, among other entities
- Progressive destruction of cartilage with deformity
- Death occurs in up to 25% of patients, due to respiratory and cardiovascular complications

Question 14: What other entity closely mimics relapsing polychondritis?

- A. Microscopic thromboangiitis
- B. Polyarteritis nodosa
- C. Hypereosinophilic syndrome
- D. Wegener’s granulomatosis
- E. Churg Strauss granuloma

Wegener’s granulomatosis

- c ANCA is positive, which is not reported in relapsing polychondritis
- On histology a true necrotizing leukocytoclastic vasculitis with granulomas is seen, unlike relapsing polychondritis
**Wegener’s granulomatosis**

- Wegener’s granulomatosis has a very similar clinical presentation
- Lung and nasal lesions occur in both entities
- WG has necrotizing vasculitis rather than primarily a lymphocytic vasculitis with primary destruction of collagen
- Otitis media can occur but external ear involvement is not present

**Summary and Conclusions**

- The vasculopathic reaction pattern is protean and can present in numerous ways
- Key categories include vascular occlusion, acute vasculitis, neutrophilic dermatoses, ‘chronic lymphocytic’ vasculitis, and granulomatous vasculitides
- Accurate diagnosis and classification requires clinicopathologic correlation