Lymphocytic Vasculitis

Anna Haemel, MD
Lindy Peta Fox, MD
24F with livedo racemosa for 1.5 years
Clinical history

• **PMH:** no history of DVT, miscarriage, or stroke
• **Medications:** oral contraceptive
• **Family History:** No hx autoimmune conditions
• **Social History:** 2 isolated episodes of cocaine use
  
  *(AFTER eruption appeared)*
Laboratory evaluation

- **P- ANCA + at 1:20; MPO antibody positive**
- **Fibrin D Dimer slightly elevated, slightly elevated Protein C**
- **Negative or within normal limits:**
  - ESR, CMP, CBC with differential
  - Urinalysis with microscopy
  - **Rheumatologic:**
    - C-ANCA/proteinase 3, ANA, dsDNA, anti-Smith, RNP, SSA, SSB, Scl-70, Jo-1, anti-phospholipid and cardiolipin antibodies, RF
  - **Immunologic:**
    - SPEP, cryoglobulins
  - **Hypercoagulable panel:**
    - PT/PTT, INR, fibrinogen, dilute RVV time, Protein S; antithrombin III, homocysteine, Factor VIII, IX and XI, MTHFR and prothrombin mutations, Factor V Leiden, Lupus anticoagulant
  - **Infectious:**
    - Hep B/C, parvovirus, PPD
Final read: “lymphocytic vasculitis”
What is this??
The enigma of lymphocytic vasculitis...

• “Few clinicians are in much doubt as to what a histopathologist’s diagnosis of leukocytoclastic vasculitis means...This situation does not obtain when a clinician receives a report of lymphocytic vasculitis. The immediate reaction might well be “huh?”

LeBoit P. *Archives of Dermatology*. 2008; 144(9): 1215-1216.
Lymphocytic vasculitis – Histopathologic definition

**Weedon**
- Lymphocytic infiltrate involving and surrounding small vessels

**LeBoit**
- Lymphocytic infiltrate involving and surrounding small vessels
  - Damage to vessel walls (e.g. fibrin deposition, lamination by pericytes)

LeBoit P. *Archives of Dermatology*. 2008; 144(9): 1215-1216.
## Lymphocytic vasculitis – Histopathologic definition

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Source of the controversy is whether observed lymphocytes are taking an active role in the vessel inflammation vs. whether they are innocent bystanders.

Lymphocytes can:
- Cause direct cytotoxic damage to endothelial cells
- Alter coagulation cascades
- Induce intimal hyperplasia
Lymphocytic vasculitis - Clinical significance is controversial

- Massa and Su
  - 71 cases of lymphocytic vasculitis
  - All met criteria for definition
    - Predominantly lymphocytic infiltrate in/around blood vessels
    - Fibrinoid necrosis of blood vessel walls
    - Endothelial cell hyperplasia
  - Clinical correlate was not “vasculitis”
    - No specific disease association found
    - Lymphocytic vasculitis may be a “pathologic end point” of many diseases

### Clinical presentation

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Clinical presentation

• LeBoit: “While it may be incredibly difficult to put together the...findings from enough cases [of lymphocytic vasculitis] to firmly document the disease in which it characteristically occurs we will be missing something if we do not try.”

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Categories of disease

- **Pernio**
- **Infection**
  - Rickettsial
  - Viral
- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren’s
  - Behcet’s
- **Vasoocclusive disease**
  - Lymphocytic thrombophilic arteritis
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Degos
- **Leukemia/malignancy**
  - Direct vessel involvement
  - Reactive processes
- **Other entities**
  - Pityriasis lichenoides
  - Resolving LCV
Categories - morphology

- **Pernio**
  - Acral purpuric papules

- **Infection**
  - Rickettsial
    - Petechiae
  - Viral
    - Exanthem

- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren’s
    - Purpuric papules
  - Behcet’s
    - Papular lesions

- **Vasoocclusive disease**
  - Lymphocytic thrombophilic arteritis
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Degos

- **Leukemia/malignancy**
  - Direct vessel involvement
  - Reactive processes

- **Other**
  - Pityriasis lichenoides
  - Resolving LCV

- **Other**
  - Infiltrated papules/nodules
  - Purpuric papules

- **Exanthem**
Categories - pathophysiology

- **Pernio**
  - Cold induced injury

- **Infection**
  - Rickettsial
  - Viral

- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren’s
  - Behcet’s

- **Vasoocclusive disease**
  - Lymphocytic thrombophilic arteritis
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  - Pityriasis lichenoides
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**Pathophysicsiology**

- Lymphocytes directed against infected endothelial cells
- Lymphocyte mediated attack on endothelial +/- epithelial cells
- Endothelial damage by lymphocytes +/- prothrombotic state \( \rightarrow \) thrombosis
- Direct vessel damage +/- reactive processes
Lymphocytic vasculitis: Suggested workup

- CBC with diff/blood smear
- ANA, ENA, ANCA
- ESR, complements
- Hypercoagulability workup (e.g. antiphospholipid antibodies)
- Infectious workup (if clinically indicated)
24F with livedo racemosa for 1.5 years
Categories - morphology

- **Pernio**: Acral purpuric papules
- **Infection**
  - Rickettsial: Petechiae
  - Viral: Exanthem
- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren’s: Purpuric papules
  - Behcet’s: Papular lesions
- **Vasoocclusive disease**
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- **Leukemia/malignancy**
  - Direct vessel involvement
  - Reactive processes
- **Other**
  - Pityriasis lichenoides
  - Resolving LCV

- Livedo racemosa
- Atrophic scarring
- Infiltrated papules/nodules
  - Purpuric papules
Categories - morphology

- Pernio: Acral purpuric papules
- Infection:
  - Rickettsial: Petechiae, Exanthem
  - Viral
- Autoimmune connective tissue diseases:
  - Lupus/Sjogren’s: Purpuric papules, Papular lesions
  - Behcet’s
- Vasoocclusive disease:
  - Lymphocytic thrombophilic arteritis
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- Leukemia/malignancy:
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- Other:
  - Pityriasis lichenoides
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- Atrophic scarring
- Livedo racemosa
- Infiltrated papules/nodules
- Purpuric papules
Lymphocytic Thrombophilic Arteritis

A Newly Described Medium-Sized Vessel Arteritis of the Skin

Joyce Siong-See Lee, MMED(UK), FAMS; Steven Kossard, FACP; Michael A. McGrath, MD, FRACP

- 5 cases in women aged 20-34
- Clinical: livedo racemosa on lower > upper extremities
- Pathology: Lymphocytic vasculitis of arterioles at subcutaneous junction with concentric fibrin ring around lumina
- Associated findings: high titer (1:320) ANA in one patient; several patients with low titer antiphospholipid antibodies; one with factor V Leiden
- No systemic disease
Lymphocytic thrombophilic vasculitis
Why is this not livedoid vasculopathy?

• Clinical
  – No purpura, ulceration, atrophie blanche, or scar

• Histopathology
  – Dense lymphocytic infiltrate
  – Hyalinized fibrin ring localized to arterioles in deep dermis and subcutis rather than small vessels

Arch Dermatol. 2008; 144 (9): 1175-82.
Lymphocytic thrombophilic vasculitis
Why is this not PAN?

• Clinical
  – No purpura, ulceration, digital necrosis
  – Pain infrequent

• Histopathology
  – Acute process (dense infiltrate, nuclear dust, luminal fibrin)
    • Fibrin present in acute stage while in PAN it is a late finding
  – No neutrophils present

Arch Dermatol. 2008; 144 (9): 1175-82.
Remaining questions...

• What is the meaning of the hypercoagulable labs in some patients?
  – May contribute to the process (BUT antiphospholipid antibodies can be an non-pathogenic epiphenomenon related to injured endothelial cells)

• Why does this patient have p-ANCA?
  – Perhaps due to cocaine but could also be part of her disease

• Is this mild chronic cutaneous PAN?

Treatment course

- Lymphocytic infiltrate $\rightarrow$ hydroxychloroquine and prednisone
- Thrombosis $\rightarrow$ ASA, pentoxifylline
Categories of disease

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• Other
  - Pityriasis lichenoides
  - Resolving LCV
Conclusions

• Primary lymphocytic vasculitis MAY exist as a disease
• By using strict, consistent criteria we may be able to achieve clinicopathologic correlation
Thank you

• Lindy Fox and Tim Berger – Mentorship
• Sarah Asch – Clinical photos and case details
• Melissa Meier and Thad Mully – Dermatopathology photos
• Dermatology Foundation – Dr. Haemel is supported by Dermatology Foundation Medical Dermatology Career Development Award
Extra slides
Lymphocytic thrombophilic arteritis
Treatment

- 1 responded to prednisolone
  - Lesions recurred after taper
  - Lesions stable off meds for 6 mo
- 1 patient - no response to low dose aspirin and clopidogrel, given warfarin - no follow up at time of writing
- 1 patient – no improvement with 6 mo low dose aspirin and nifedipine, lesions progressed. On warfarin
- 1 patient low dose aspirin with no response, stable off treatment
- 1 patient - lost to follow-up
BRIEF REPORT

Lymphocytic thrombophilic arteritis presenting as localized livedo racemosa

Shally Gupta, Adrian Mar, John P Dowling and Peter Cowen

Skin and Cancer Foundation, Carlton, and Departments of Dermatology and Anatomical Pathology, Monash Medical Centre, Clayton, Victoria, Australia

A 28-year-old Costa Rican woman presented with a 6-year history of an asymptomatic progressive localized livedo racemosa on her limbs. Histological examination revealed a lymphocytic vasculitis targeting the arterioles in the deep dermis. In addition, a distinct hyalinised fibrin ring was noted at the periphery of the vessel lumen. These findings were consistent with the recently described entity known as lymphocytic thrombophilic arteritis. An extensive array of investigations did not show any underlying systemic disease, and the patient has remained in good health without treatment.
Figure 1 Clinical presentation. (a) Localized livedo racemosa over the lower limbs, and (b) the left ankle.
Macular arteritis
Cutaneous arteritis presenting with hyperpigmented macules: Macular arteritis

Howard Fein, MD, a, * Anita P. Sheth, MD, a, b and Diya F. Mutasim, MD a

Cincinnati, Ohio

Macular arteritis is a novel form of cutaneous arteritis in which the primary lesion is a hyperpigmented macule. Traditional stigmata of cutaneous vasculitis such as palpable purpura and erythematous nodules are not present. The disease is asymptomatic and appears to follow an indolent course. Systemic involvement has not been observed. (J Am Acad Dermatol 2003;49:519-22.)
Macular lymphocytic arteritis: a unique benign cutaneous arteritis, mediated by lymphocytes and appearing as macules

- Females (70%), mean 41 years old, African American (50%)
- Macules hyperpigmented > hypopigmented, erythematous
- No livedo racemosa
- Asymptomatic to mildly pruritic
- Lower extremities (100%) > upper extremities (44%)
- Histopathology
  - Lymphocytic vasculitis of artery in deep dermis/subcutis
  - Intimal thickening
  - Fibrinoid ring in the lumen
  - Intact internal elastic lamina
- Limited to the skin
Macular lymphocytic arteritis: a unique benign cutaneous arteritis, mediated by lymphocytes and appearing as macules

- **Laboratory findings**
  - Weakly pos anticardiolipin Ab (2/7)
  - ANA pos (1/7)
  - Anti-SS-A pos (1/7)

- **No systemic disease in any patient**
“Macular Arteritis”: A Latent Form of Cutaneous Polyarteritis Nodosa?

Wael Al-Daraji, MBBS, MSc, MRCP, MD,* A. Neal Gregory, MPH, MD,† and J. Andrew Carlson, MD, FRCPC‡

“Macular Arteritis”: A Latent Form of Cutaneous Polyarteritis Nodosa?

Wael Al-Daraji, MBBS, MSc, MRCP, MD,* A. Neal Gregory, MPH, MD,† and J. Andrew Carlson, MD, FRCPC‡

• Case had
  – Clinical findings
    • Most similar to macular arteritis
  – Histopathologic findings with features of cPAN
    • Destruction of internal elastic lamina

• Is macular arteritis a form of cPAN that is chronic, but mild with less vascular injury?
  – No nodules clinically
  – Retain an intact internal elastic lamina
Paraneoplastic vasculitis
Cutaneous Lymphocytic Vasculopathy in Lymphoproliferative Disorders—A Paraneoplastic Lymphocytic Vasculitis of the Skin

NICHOLAS A. PAVLIDIS, GEORGE KLOUVAS, MARIA TSOKOS, MARIA BAI, and HARALAMPOS M. MOUTSOPOULOS

- 91 pts with NHL and 25 pts with CLL followed
- 11 patients with lymphocytic vasculitis
- Papular eruptions (5), maculopapular (3), palpable purpura (3)
- Pruritus (10)
- 18 months between diagnosis of lymphoproliferative disease and lymphocytic vasculitis
Paraneoplastic Lymphocytic Vasculitis

• Autoimmune diseases associated
  – Autoimmune hemolytic anemia (2)
  – Arthralgias of hands (2)
  – Peripheral neuropathy (2)
  – Raynaud’s phenomenon (1)

• Episodes of lymphocytic vasculitis
  – 1-4 episodes
  – Duration 2-12 weeks
  – Recurrent episodes in patients with partial remission or stable or progressive disease control (cancer)

Paraneoplastic Lymphocytic Vasculitis

• **Histopathology**
  – Perivascular infiltration of lymphoplasmocytic cells around small vessels
  – Vessel wall infiltration with few PMNs but no leukocytoclasia
  – No tumor cells seen

• **Autoimmune profiles**
  – ANA (2), dsDNA neg, anti-ENA neg
  – Cryoglobulins negative
  – IgG and IgM anticardiolipin AB increased

Cutaneous lymphocytic vasculitis in acute myeloid leukaemia

A.M. FARRELL, C. GOOPTU, D. WOODROW, * C. COSTELLO, † C. B. BUNKER AND J. J. CREAM

Departments of Dermatology, *Histopathology and †Haematology, Charing Cross and Westminster Medical School, London, U.K.

Accepted for publication 2 November 1995
Acute lymphoblastic leukaemia presenting as vasculitis

Gupta A et al. BJH 2005; 132:384
Clinical and Laboratory Observations

Cutaneous Lymphocytic Vasculitis as the Presenting Feature of Acute Lymphoblastic Leukemia

Tang-Her Jaing, M.D., Chuen Hsueh, M.D., Cheng-Hsun Chiu, M.D., Ph.D., I-Hsin Shih, M.D., Chin-Kan Chan, M.D., and Iou-Jih Hung, M.D.
Paraneoplastic Lymphocytic Vasculitis
Conclusions

• B- and T-cell leukemias and lymphomas (CLL, ALL, AML, NHL)
• T-cell mediated
General Slides
Differential diagnosis

- Antiphospholipid antibody syndrome
- Livedoid vasculopathy
- Cutaneous polyarteritis nodosa
- Levamisole contaminated cocaine exposure
- ANCA+ vasculitis
- Cryoglobulinemia
- Sneddon syndrome
- Degos
Lymphocytic Vasculitis
Histopathologic Definition

• Lymphocytic infiltrate that involves and surrounds walls of small vessels in the dermis
• Associated endothelial cell swelling
• Extravasation of erythrocytes
• Nuclear dust is uncommon
• Some authors require the presence of
  – Vessel wall destruction
  – Fibrin deposition
  – Hemorrhage

Weedon D. In: Skin Pathology, 3rd Ed, 2010
Lymphocytic Vasculitis
Role of the lymphocyte?

• Lymphocytes can
  – Use cell surface receptors to track to targets
  – Can recruit other cell types
  – Mediate acute cytotoxic reactions
  – Sustain chronic inflammation

• Lymphocytes mediate chronic damage to endothelial cells, leading to
  – Fibrin deposition
  – Hypercoagulability
  – Intimal hyperplasia

Kossard S. Australasian Journal of Dermatology. 2000; 41: 149
Lymphocytic Vasculitis
Role of the lymphocyte?

• Pure lymphocytic (vs. neutrophilic vs. granulomatous) vasculitis is an artificial concept and these infiltrates are not mutually exclusive
  – It is possible that in vasculitis, lymphocytes are the primary pathologic process and neutrophils and leukocytoclasis are secondary processes
  – In late lesions of leukocytoclastic vasculitis, lymphocytes may be the predominant cell type

Kossard S. Australasian Journal of Dermatology. 2000; 41: 149