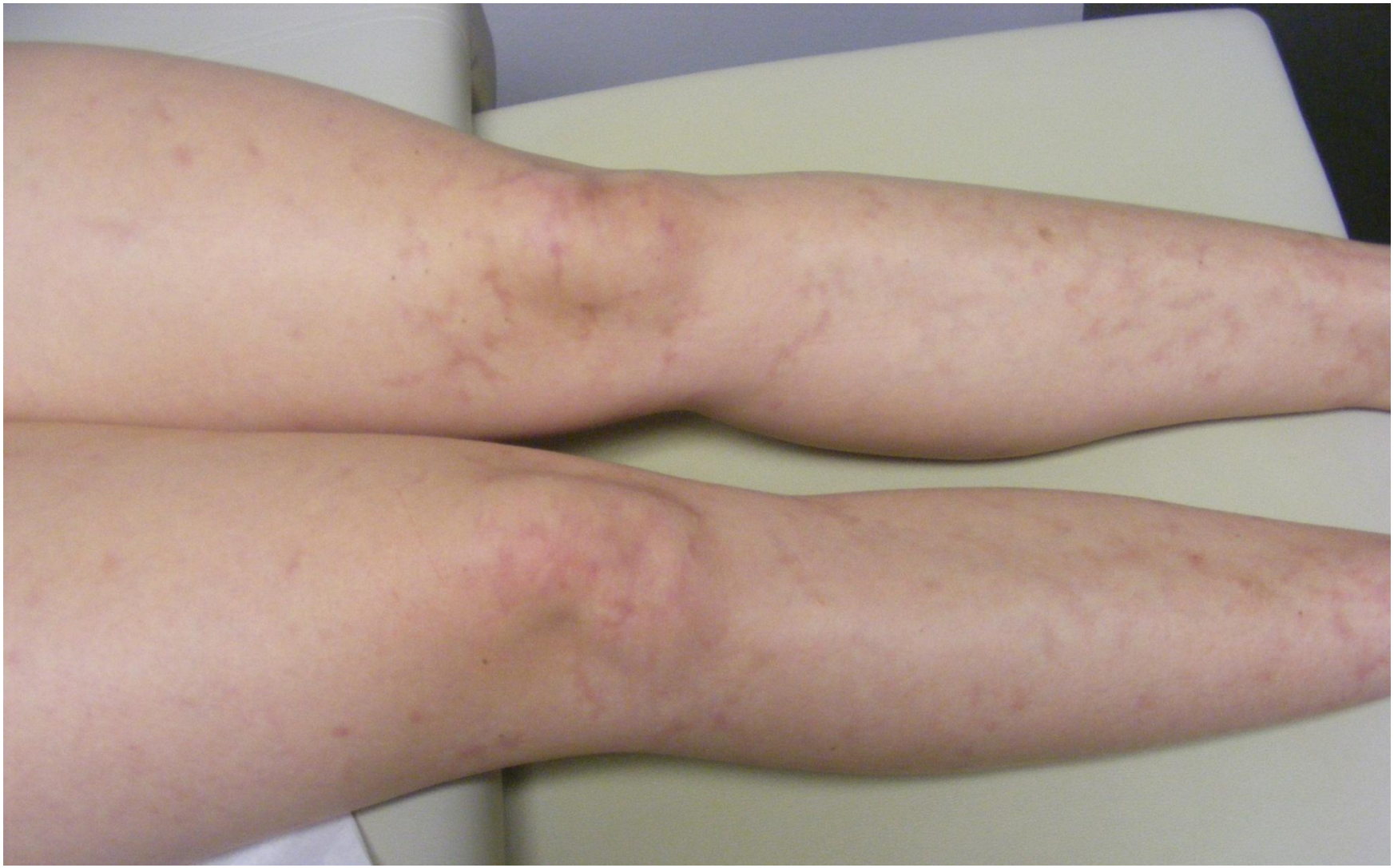
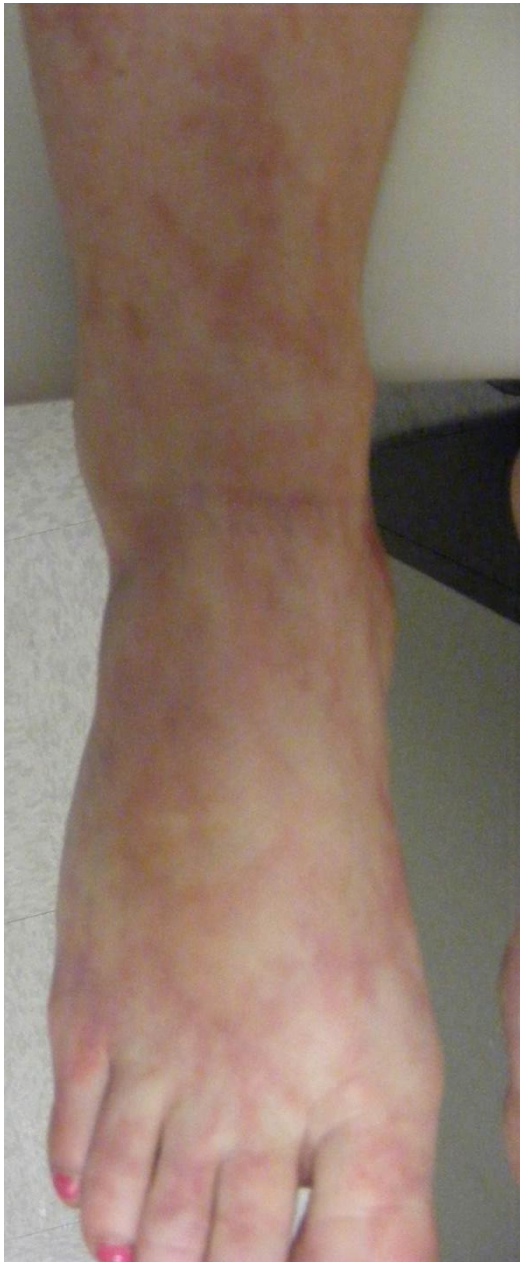
Lymphocytic Vasculitis

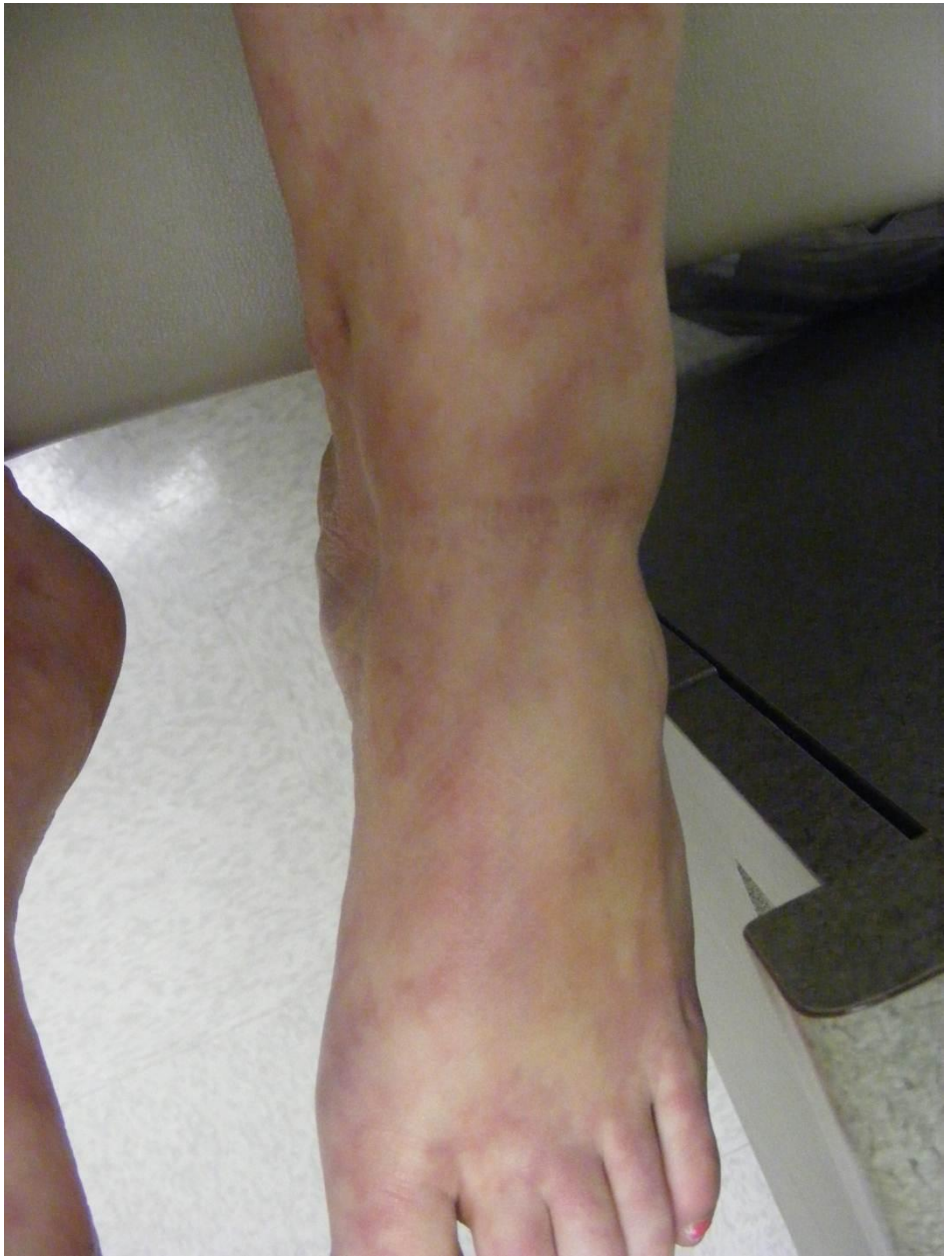
Anna Haemel, MD

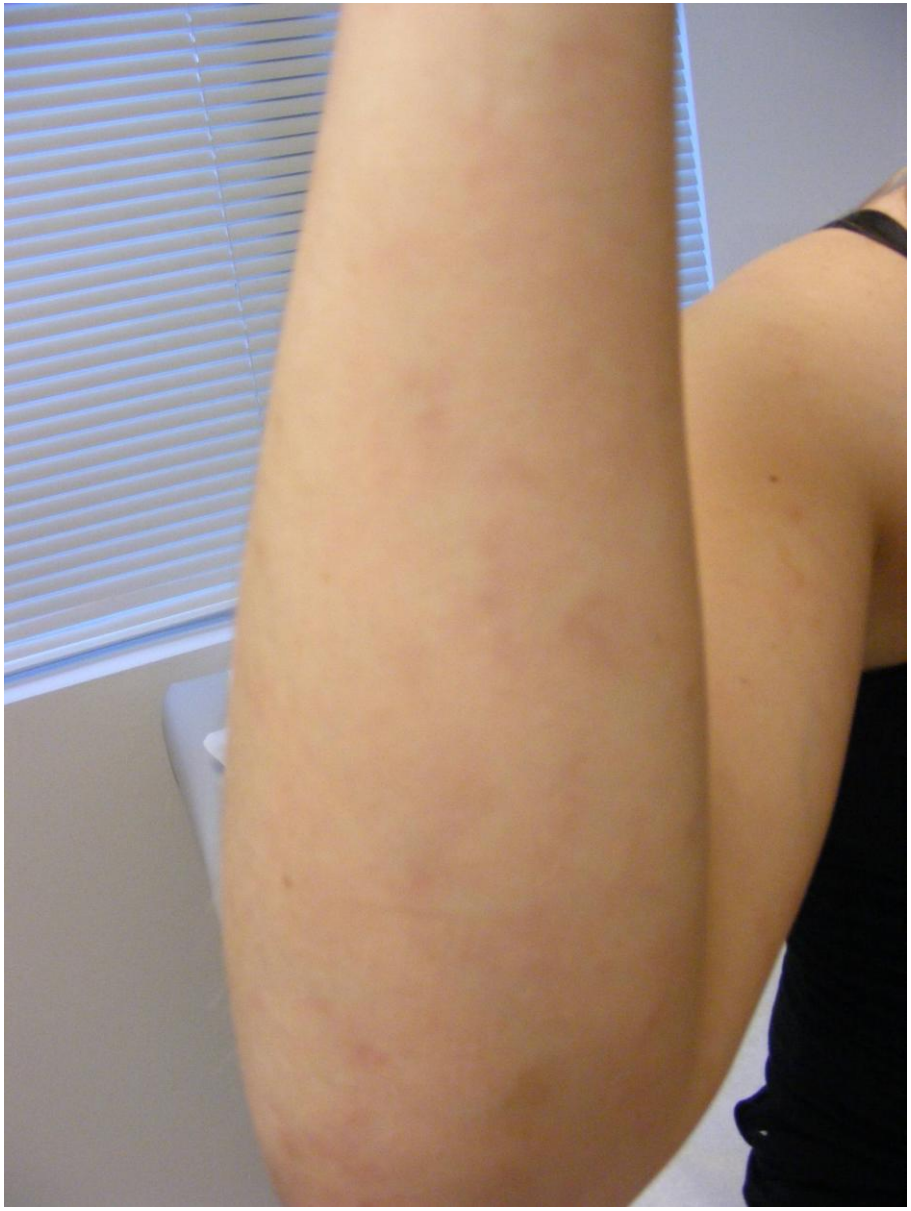
Lindy Peta Fox, MD

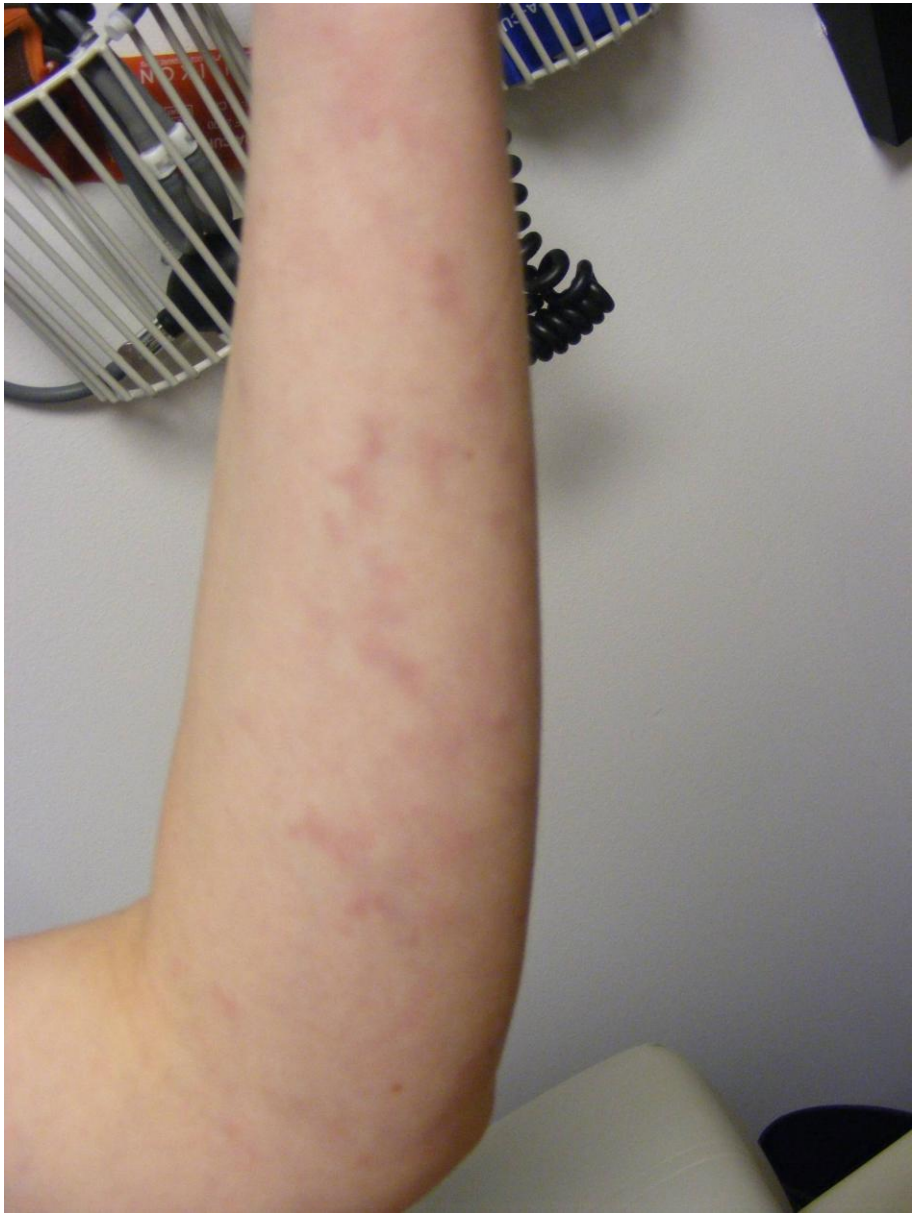
24F with livedo racemosa for 1.5 years









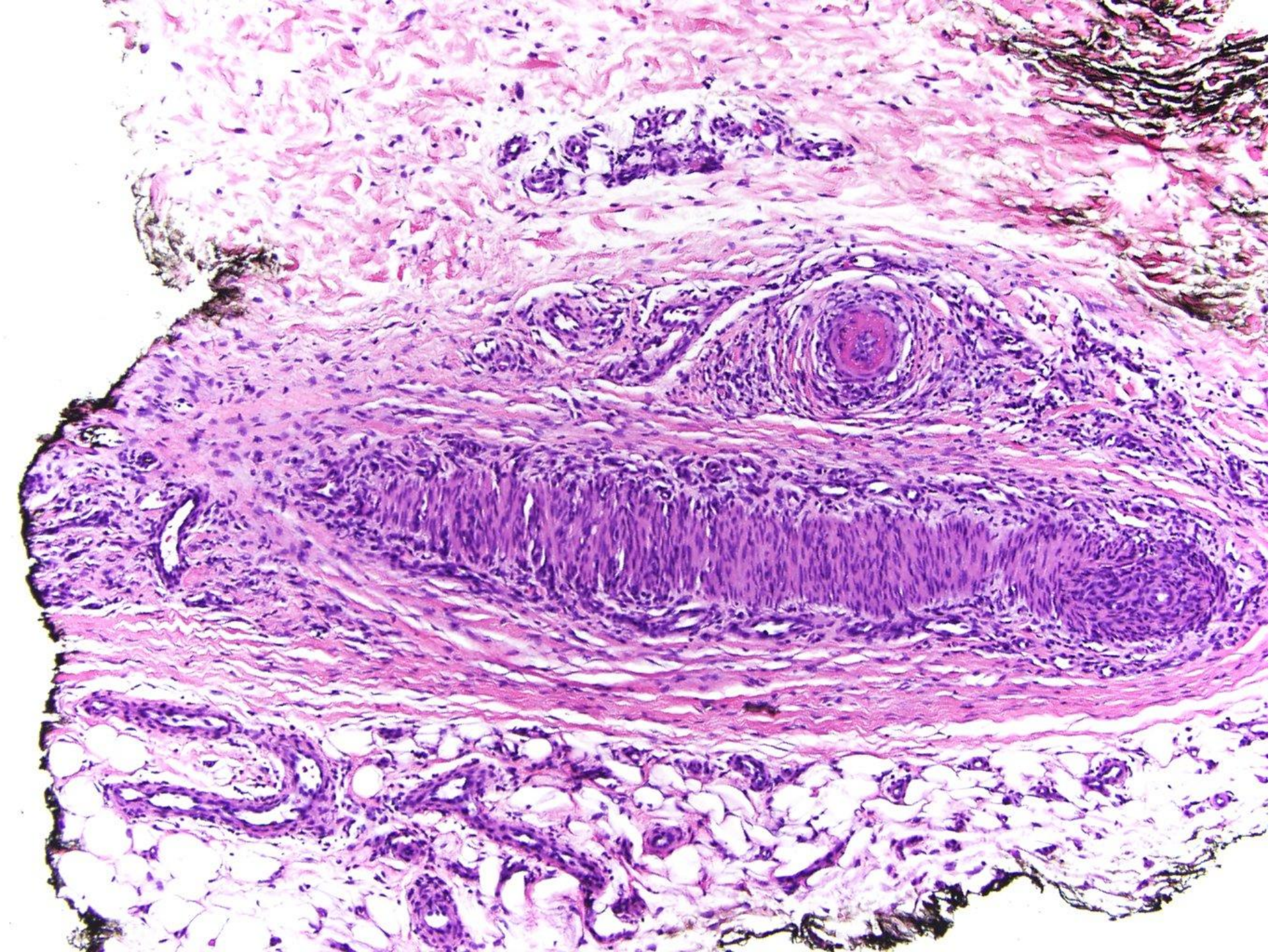


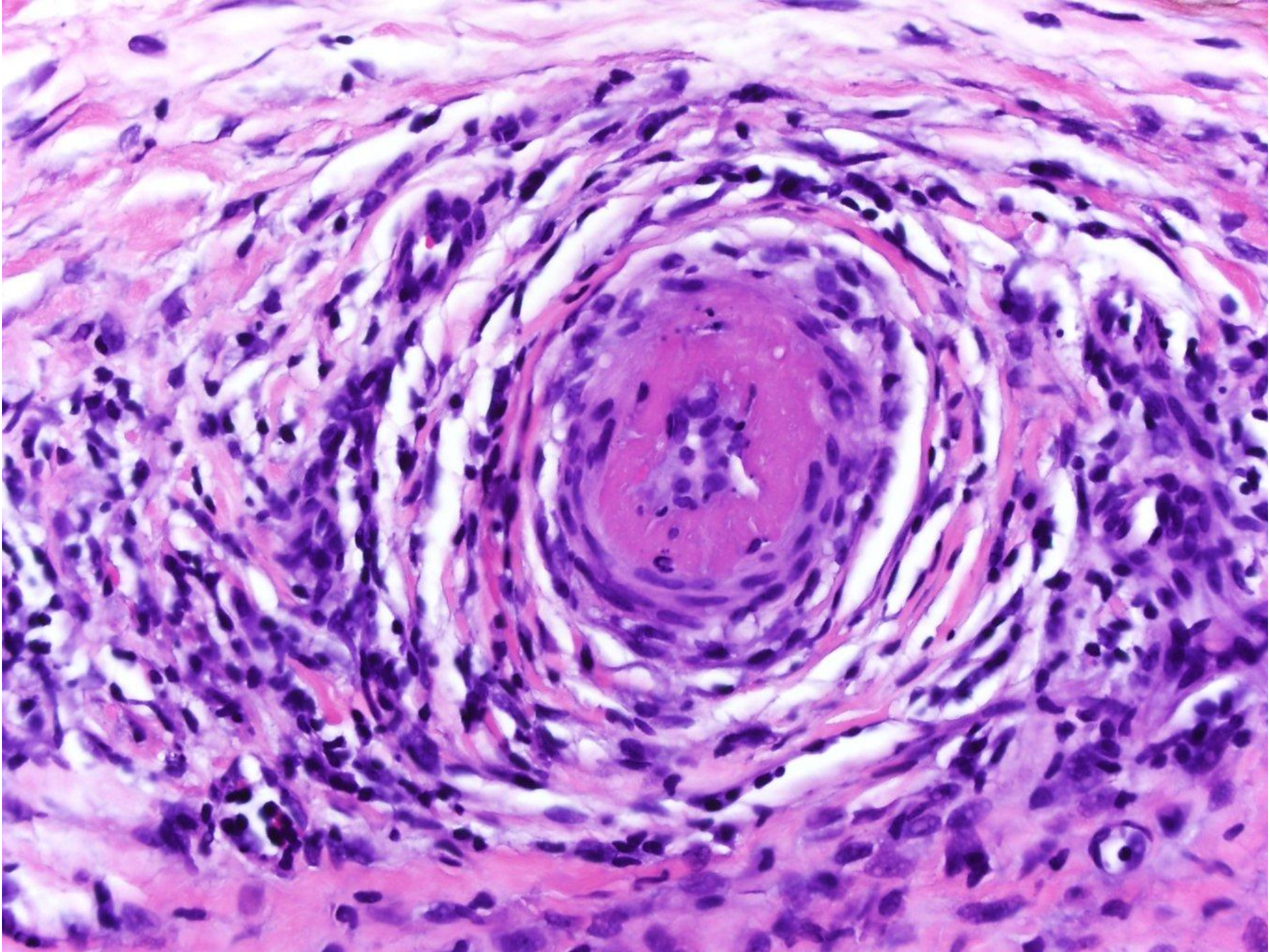
Clinical history

- **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

AND

- Damage to vessel walls (e.g. fibrin deposition, lamination by pericytes)

Weedon D. In: *Skin Pathology*, 3rd Ed, 2010.
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

  AND

- Damage to vessel walls (e.g. fibrin deposition, lamination by pericytes)

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

Massa M and Su W. *J Cut Pathol*. 1984; 11:132-9.

Clinical presentation

Weedon

- **Pernio**
- **Rickettsial/viral infections**
- Connective tissue disease
- Degos
- Sneddon syndrome
- Lymphoproliferative disease
- Pityriasis lichenoides
- Pyoderma gangrenosum
- Viral infections
- Pigmented purpuric dermatoses
- Gyrate and annular erythemas
- Polymorphous light eruption
- PUPP
- TRAPS

LeBoit

- **Pernio**
- **Rickettsial infections**
- Connective tissue disease
- Degos
- Sneddon syndrome
- Lymphoproliferative disease
- Pityriasis lichenoides
- Nonspecific infiltration (e.g. pyoderma gangrenosum)
- Herpetic infection
- Drug reactions
- Bites and stings/scabies nodules
- Resolving LCV
- Lymphocytic thrombophilic vasculitis

Weedon D. In: *Skin Pathology*, 3rd Ed, 2010.
Carlson J, et al. *Seminars in Diagnostic Pathology*. 1996; 13 (1): 72-90.

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***.”

LeBoit P. *Archives of Dermatology*. 2008; 144(9): 1215-1216.

Clinical presentation

Weedon

- **Pernio**
- **Rickettsial/viral infections**
- Connective tissue disease
- Degos
- Sneddon syndrome
- Lymphoproliferative disease
- Pityriasis lichenoides
- Pyoderma gangrenosum
- Viral infections
- Pigmented purpuric dermatoses
- Gyrate and annular erythemas
- Polymorphous light eruption
- PUPP
- TRAPS

LeBoit

- **Pernio**
- **Rickettsial infections**
- Connective tissue disease
- Degos
- Sneddon syndrome
- Lymphoproliferative disease
- Pityriasis lichenoides
- Nonspecific infiltration (e.g. pyoderma gangrenosum)
- Herpetic infection
- Drug reactions
- Bites and stings/scabies nodules
- Resolving LCV
- Lymphocytic thrombophilic vasculitis

Weedon D. In: *Skin Pathology*, 3rd Ed, 2010.
Carlson J, et al. *Seminars in Diagnostic Pathology*. 1996; 13 (1): 72-90.

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**
- **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**

  -Pityriasis lichenoides

  -Resolving LCV

Acral purpuric papules

Petechiae
Exanthem

Purpuric papules
Papular lesions

Livedo racemosa

Atrophic scarring

Infiltrated papules/nodules
Purpuric papules

Categories - pathophysiology

- **Pernio** — Cold induced injury
- **Infection**
  - Rickettsial
  - Viral

  Lymphocytes directed against infected endothelial cells
- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren's
  - Behcet's

  Lymphocyte mediated attack on endothelial +/- epithelial cells
- **Vasoocclusive disease**
  - Lymphocytic thrombophilic arteritis
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Degos

  Endothelial damage by lymphocytes +/- prothrombotic state → thrombosis
- **Leukemia/malignancy**
  - Direct vessel involvement
  - Reactive processes

  Direct vessel damage +/- reactive processes
- **Other**

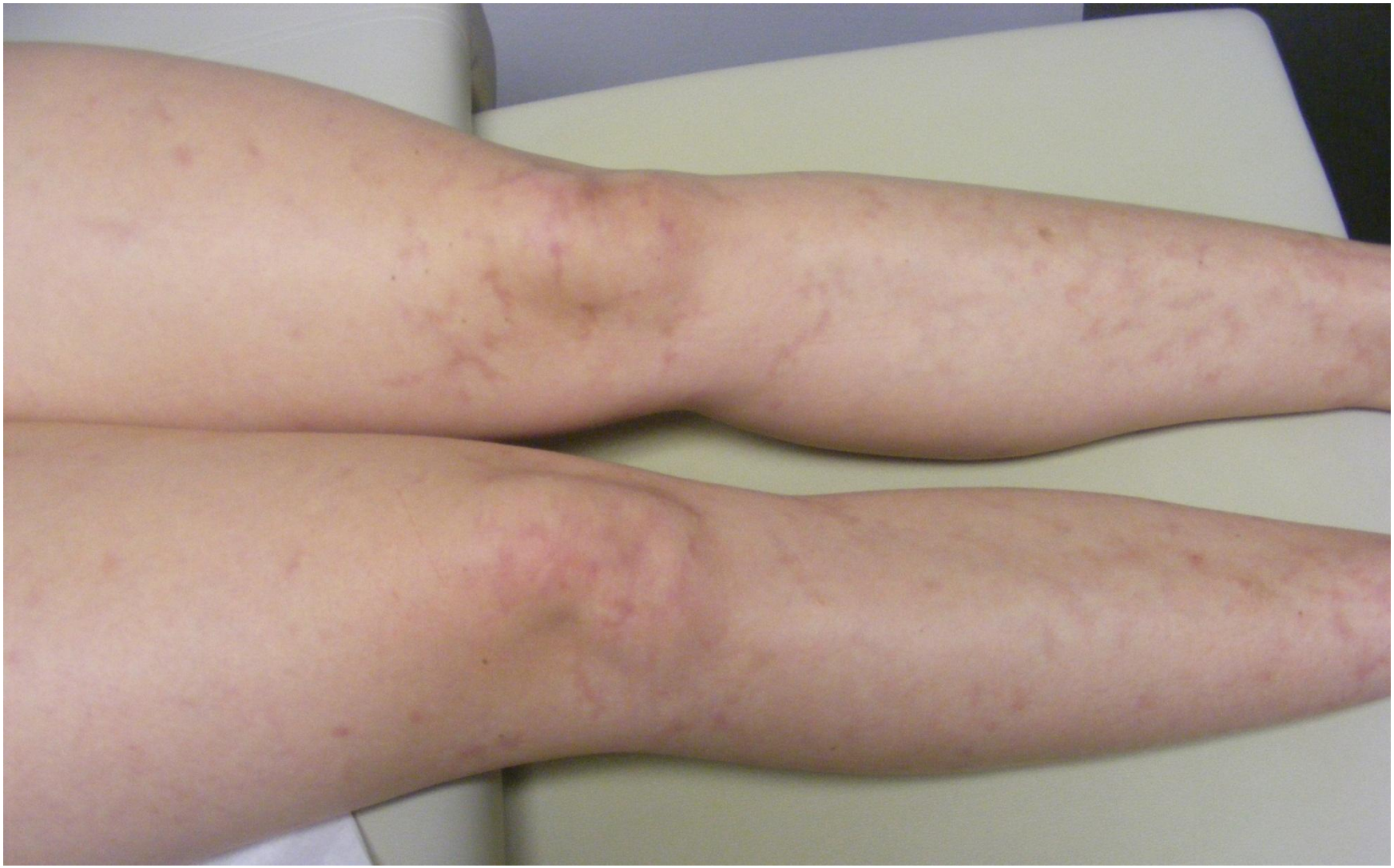
  -Pityriasis lichenoides

  -Resolving LCV

Lymphocytic vasculitis: Suggested workup

- CBC with diff/blood smear
- ANA, ENA, ANCAs
- ESR, complements
- Hypercoagulability workup (e.g. antiphospholipid antibodies)
- Infectious workup (if clinically indicated)

24F with livedo racemosa for 1.5 years



Categories - morphology

- **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**

  -Pityriasis lichenoides

  -Resolving LCV

Acral purpuric papules

Petechiae
Exanthem

Purpuric papules
Papular lesions

Livedo racemosa

Atrophic scarring

Infiltrated papules/nodules
Purpuric papules

Categories - morphology

- **Pernio** — Acral purpuric papules
- **Infection**
  - Rickettsial
  - Viral

  Petechiae
  Exanthem
- **Autoimmune connective tissue diseases**
  - Lupus/Sjogren's
  - Behcet's

  Purpuric papules
  Papular lesions
- **Vasoocclusive disease**
  - **Lymphocytic thrombophilic arteritis**
  - Sneddon syndrome
  - Livedoid vasculopathy
  - Degos

  Livedo racemosa

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

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

  -Pityriasis lichenoides

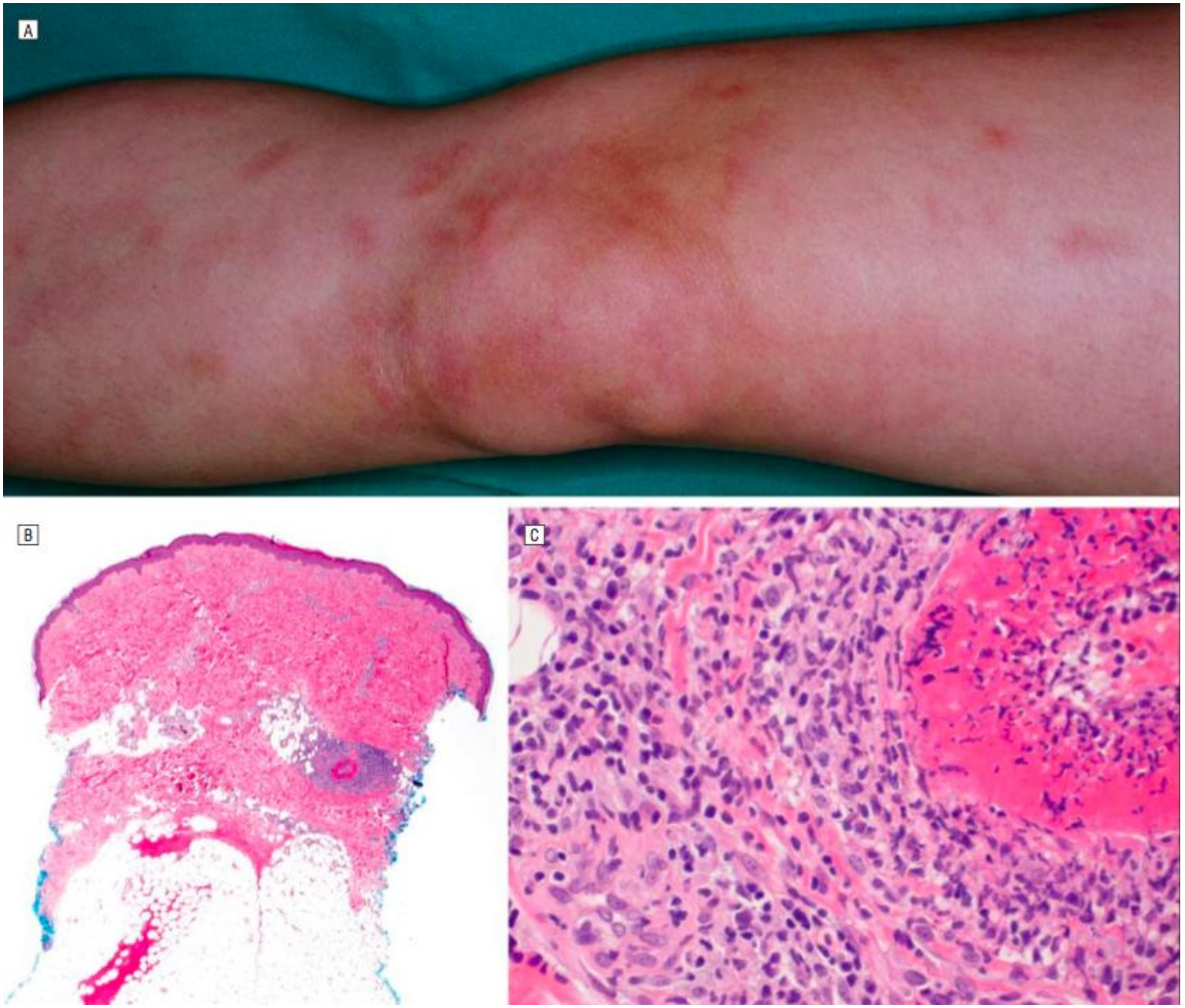
  -Resolving LCV

Lymphocytic Thrombophilic Arteritis

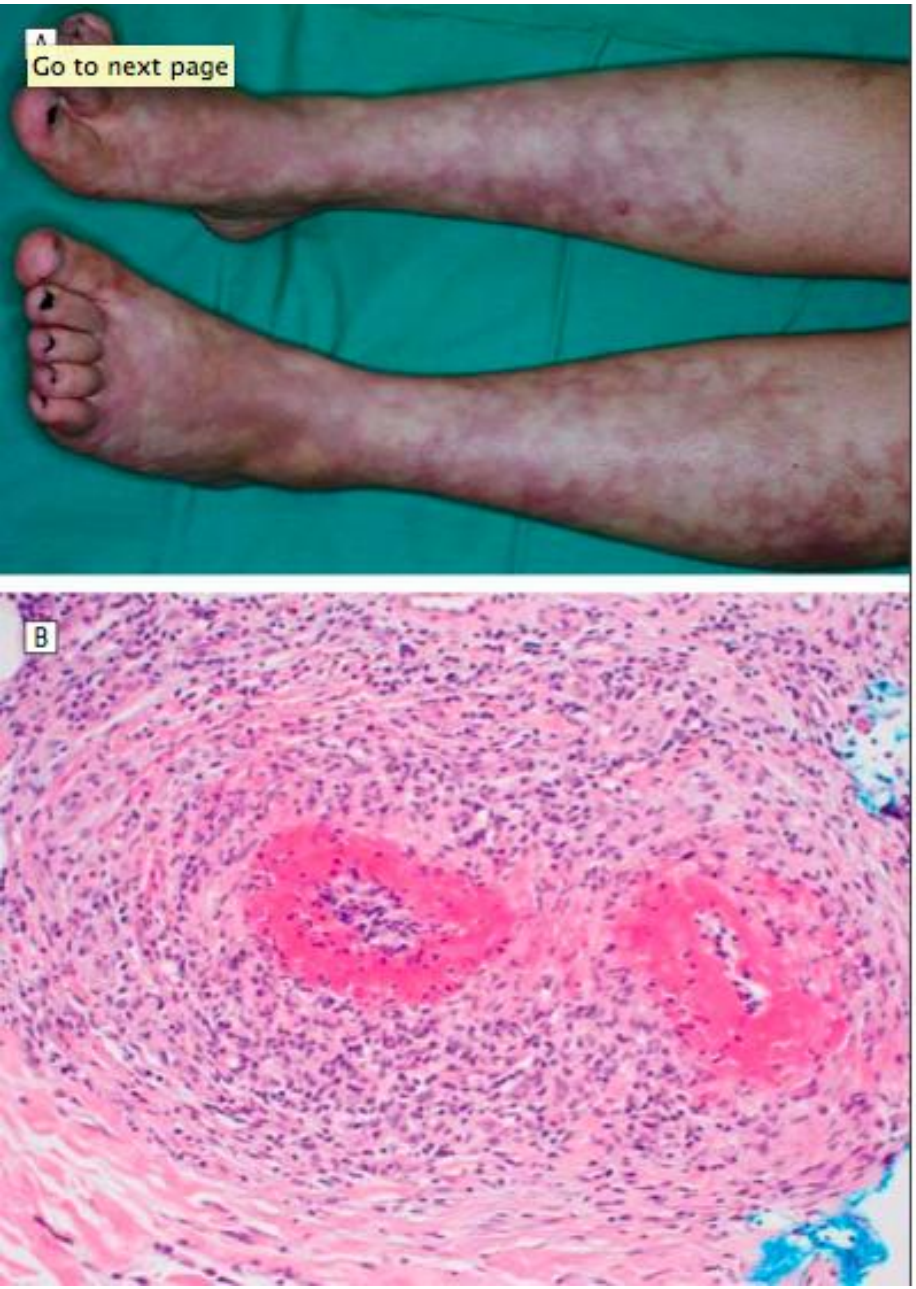
A Newly Described Medium-Sized Vessel Arteritis of the Skin

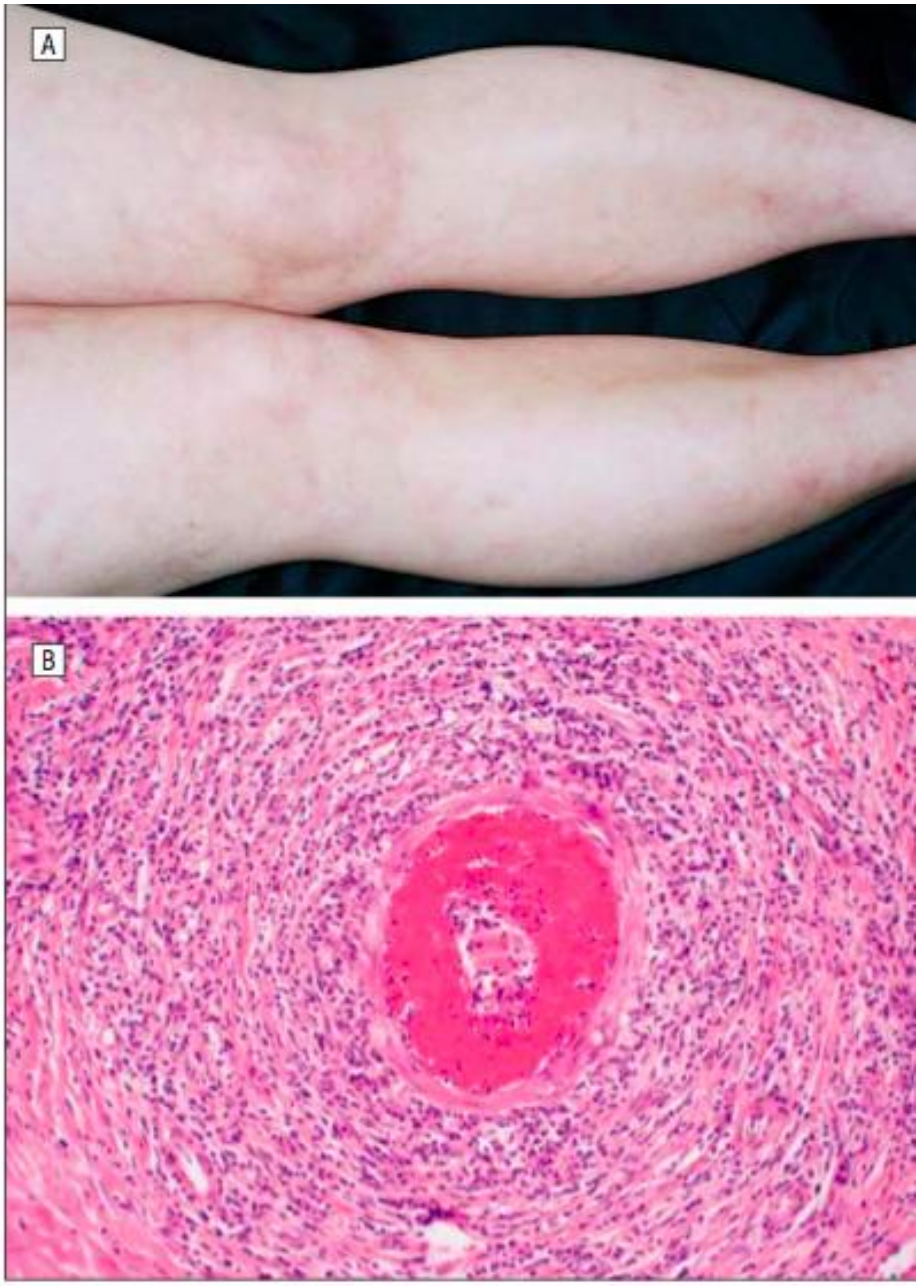
Joyce Siong-See Lee, MMED(UK), FAMS; Steven Kossard, FACD; Michael A. McGrath, MD, FRACP

- 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



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





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

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?

Lamprecht P et al. *Rheumatology.* 2000; 39 (5): 568-570.
Waller, JM et al. *Journal of the American Academy of Dermatology*. 2010; 63 (3): 530–535.

Treatment course

- Lymphocytic infiltrate → hydroxychloroquine and prednisone
- Thrombosis → ASA, pentoxifylline

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**

  -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

OBSERVATION

Lymphocytic Thrombophilic Arteritis

A Newly Described Medium-Sized Vessel Arteritis of the Skin

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

- **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

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

Australasian Journal of Dermatology (2011) 52, 52–55 doi: 10.1111/j.1440-0960.2010.00673.x

BRIEF REPORT

Lymphocytic thrombophilic arteritis presenting as localized livedo racemosa

Shally Gupta,[1] Adrian Mar,[2] John P Dowling[3] and Peter Cowen[2]

[1]*Skin and Cancer Foundation, Carlton, and Departments of* [2]*Dermatology and* [3]*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.

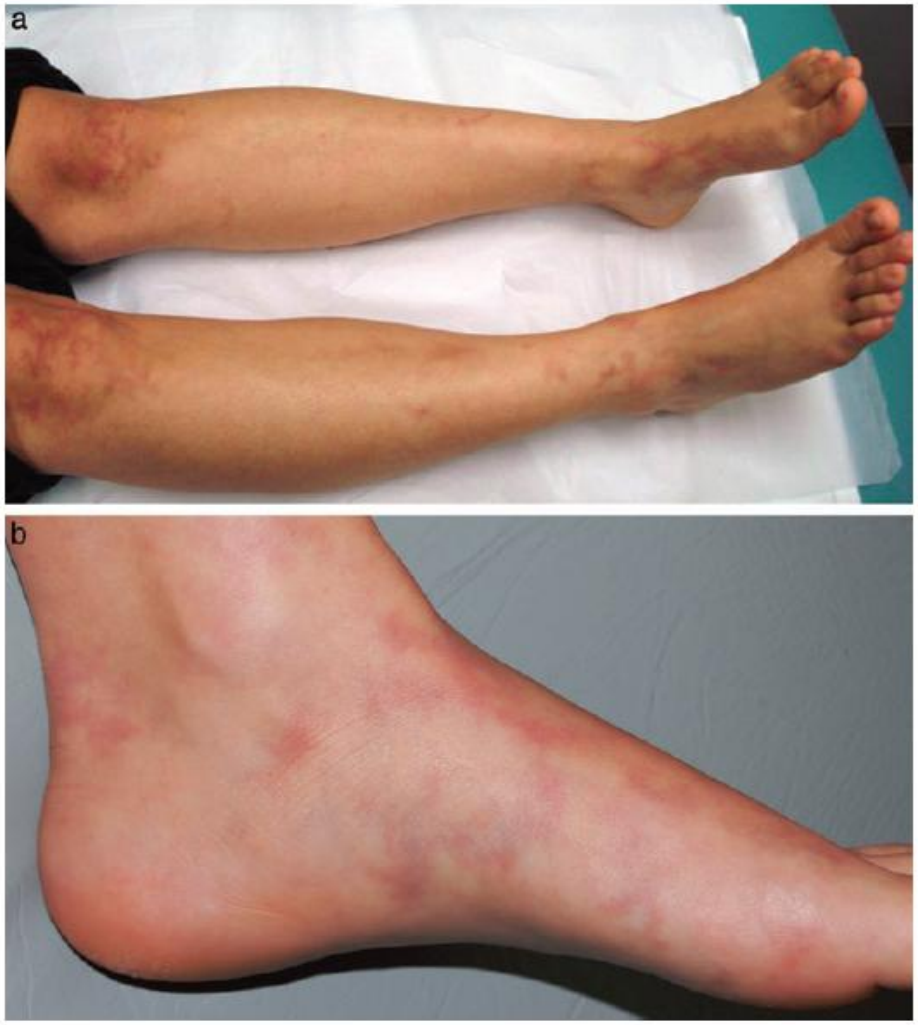
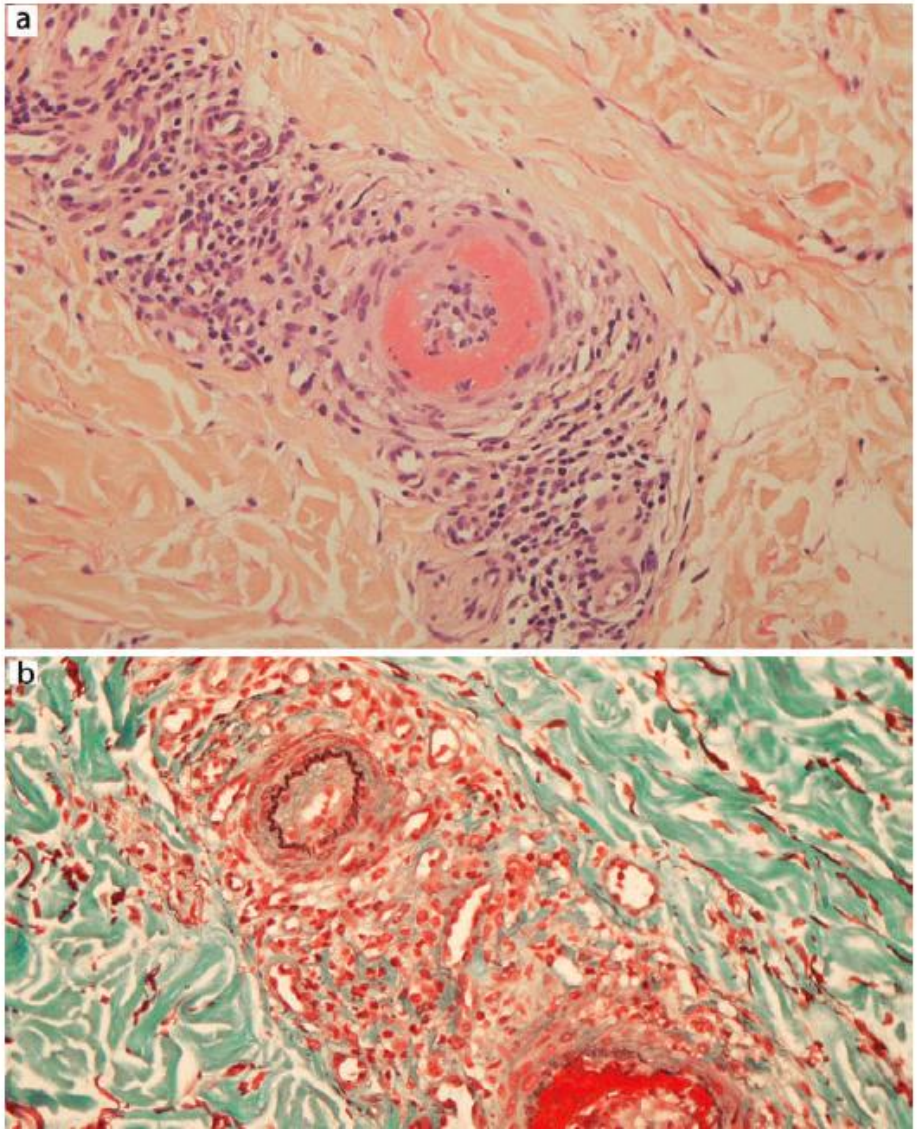


Figure 1 Clinical presentation. (a) Localized livedo racemosa over the lower limbs, and (b) the left ankle.

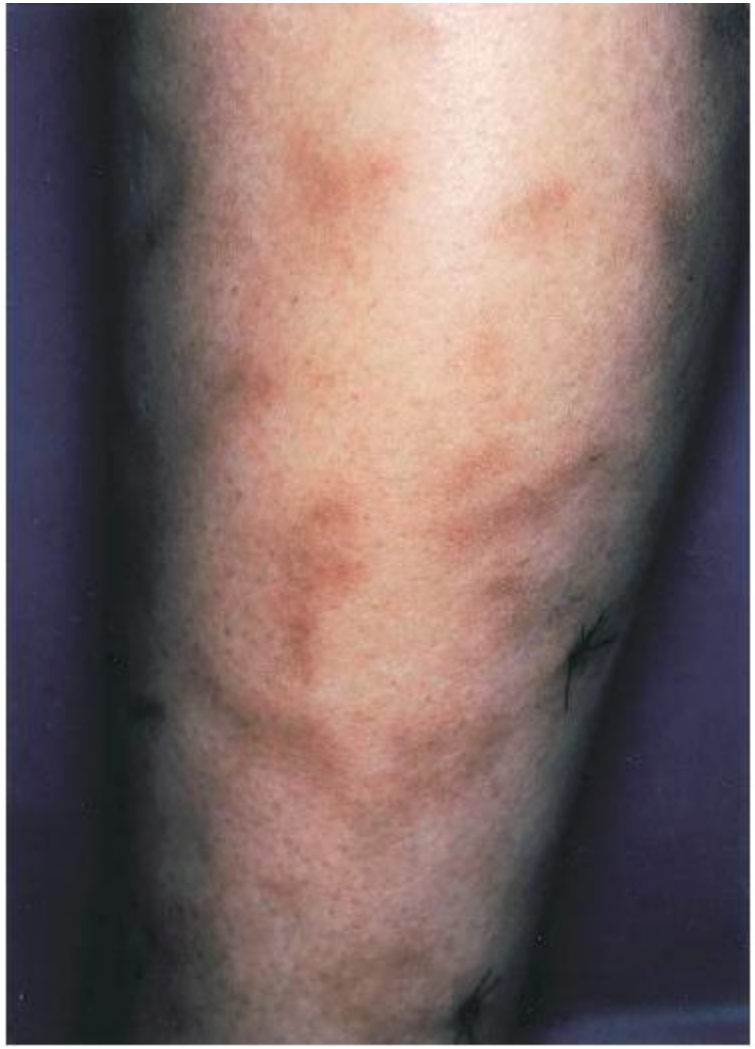


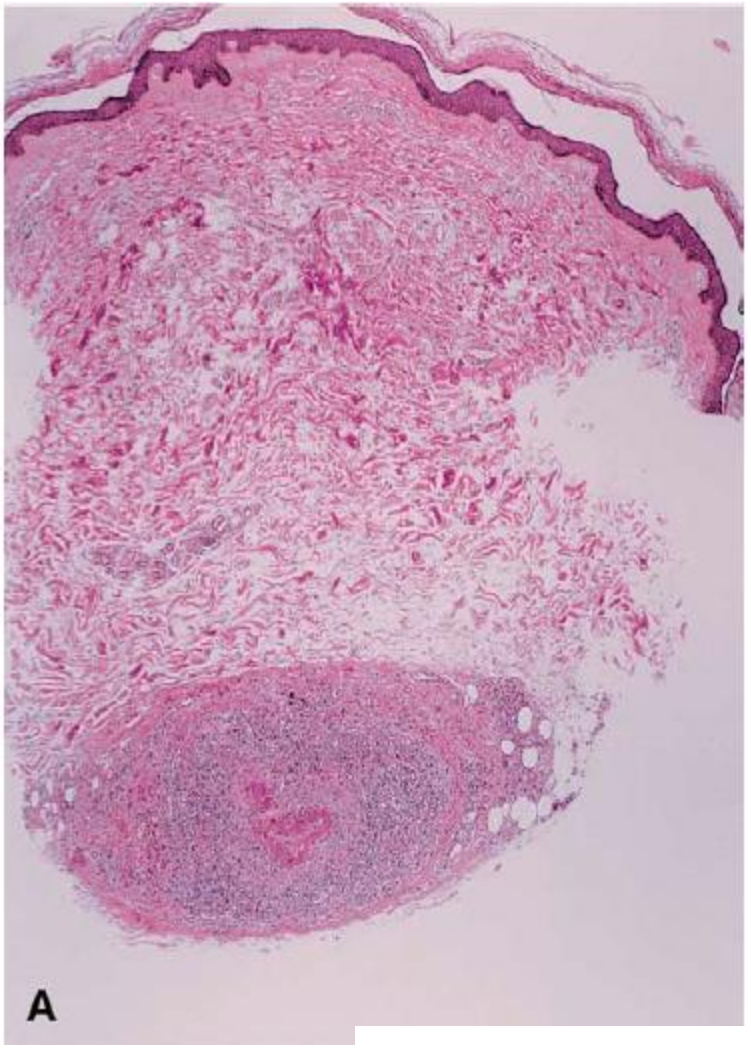
Macular arteritis

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.)





J Am Acad Dermatol
September 2003

J Cutan Pathol 2009: 36: 1269–1274
doi: 10.1111/j.1600-0560.2009.01272.x
[Correction added after online publication 22 June 2009: amendment of doi]
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

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

Saleh and Mutasim. J Cutan Pathol 2009; 36: 1269-74

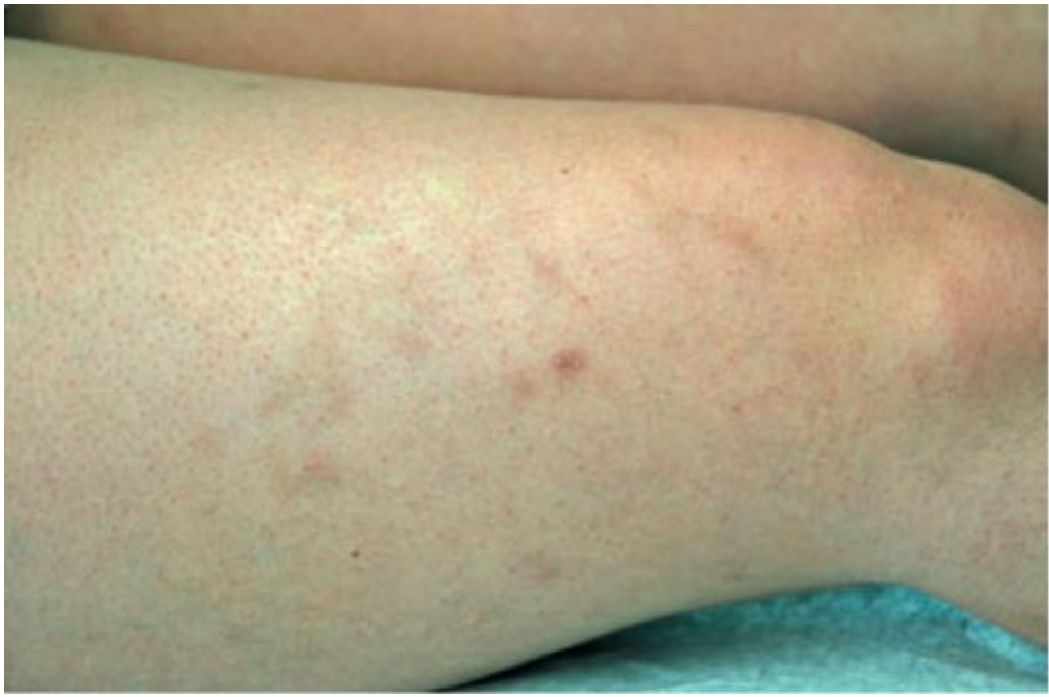
J Cutan Pathol 2009: 36: 1269–1274
doi: 10.1111/j.1600-0560.2009.01272.x
[Correction added after online publication 22 June 2009: amendment of doi]
John Wiley & Sons. Printed in Singapore

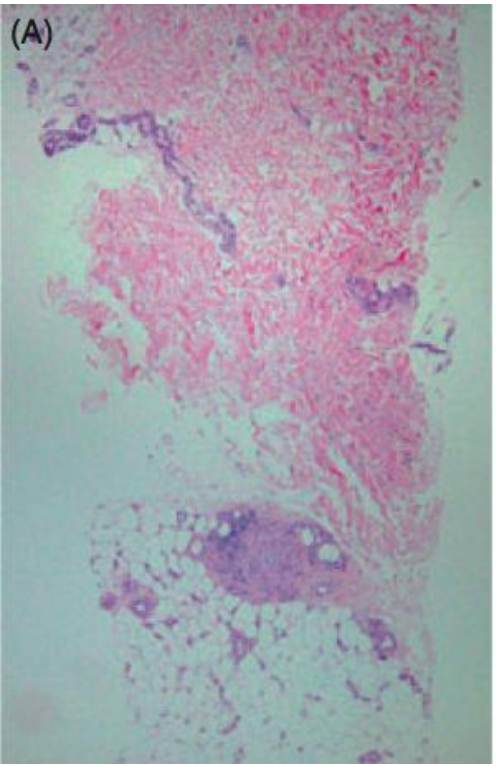
Journal of
Cutaneous Pathology

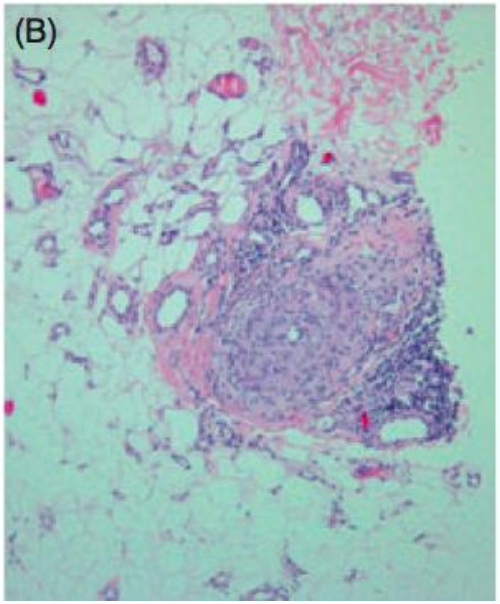
Macular lymphocytic arteritis: a unique benign cutaneous arteritis, mediated by lymphocytes and appearing as macules

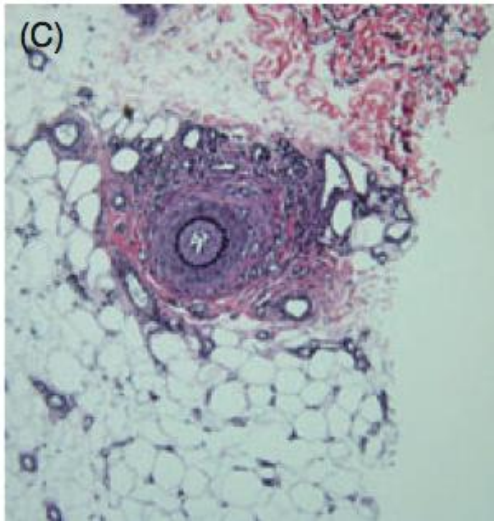
- Laboratory findings
  - Weakly pos anticardiolipin Ab (2/7)
  - ANA pos (1/7)
  - Anti-SS-A pos (1/7)
- No systemic disease in any patient

Saleh and Mutasim. J Cutan Pathol 2009; 36: 1269-74

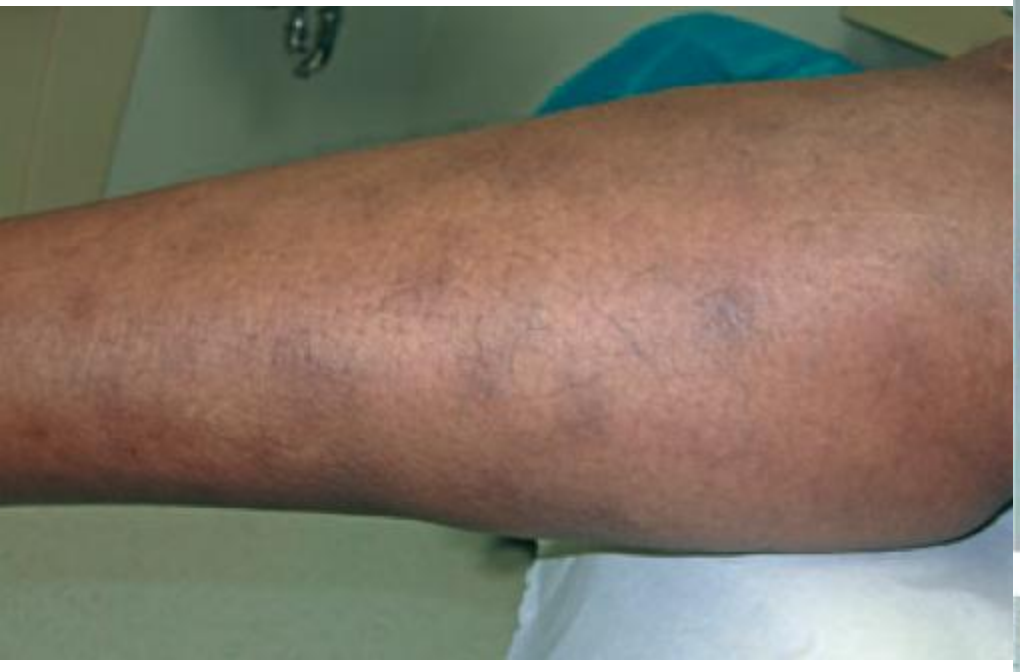


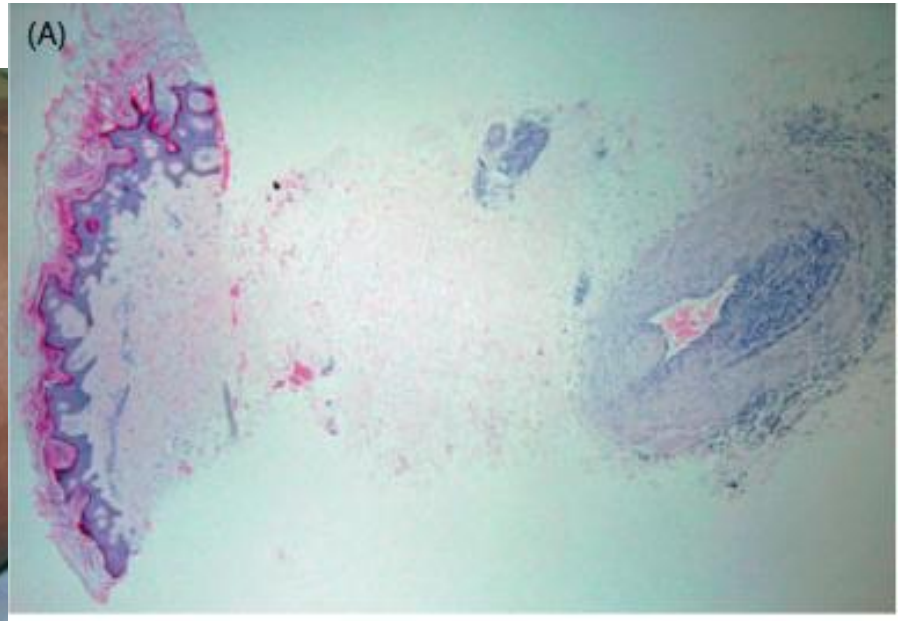


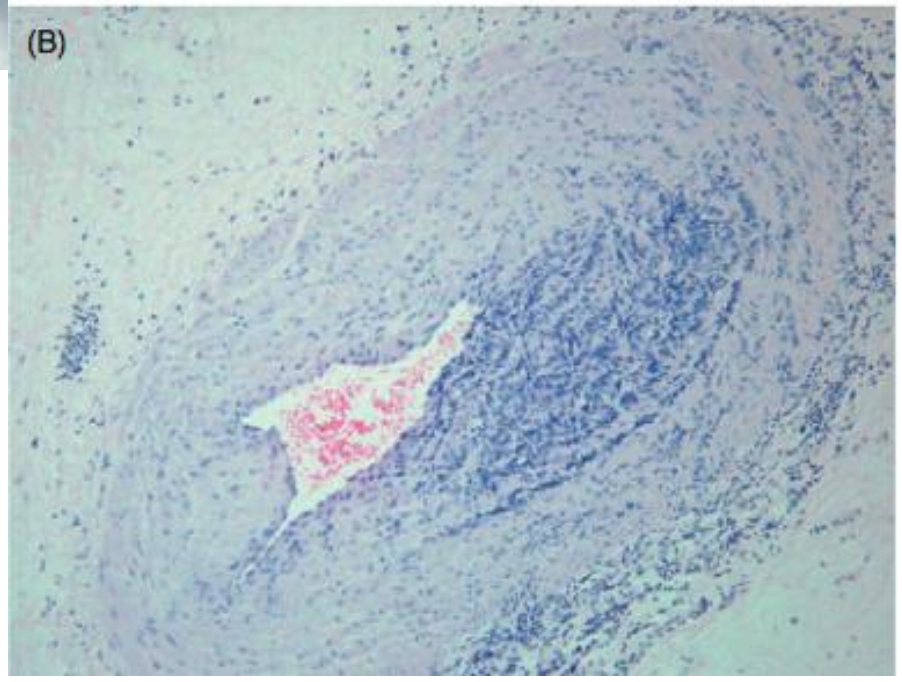




Saleh and Mutasim. J Cutan Pathol 2009; 36: 1269-74



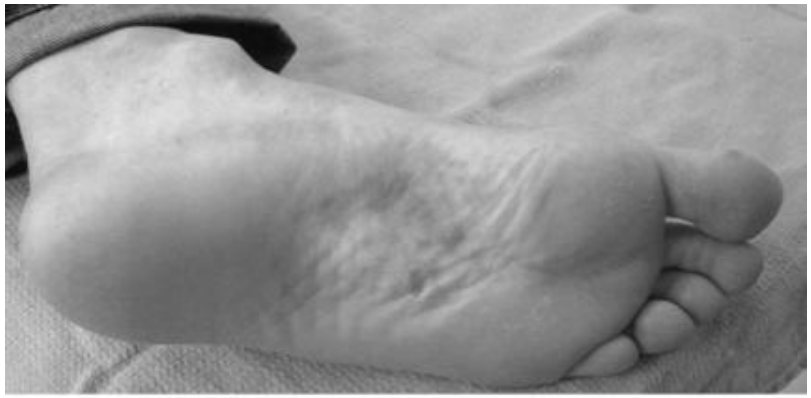


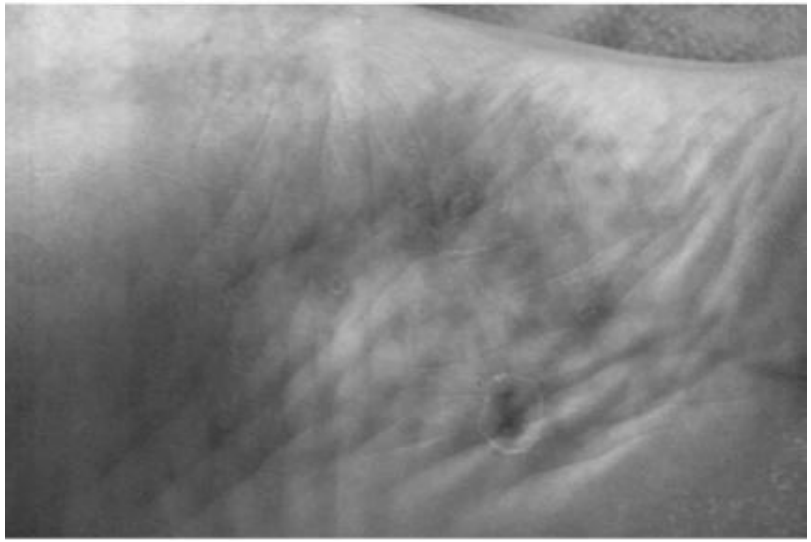


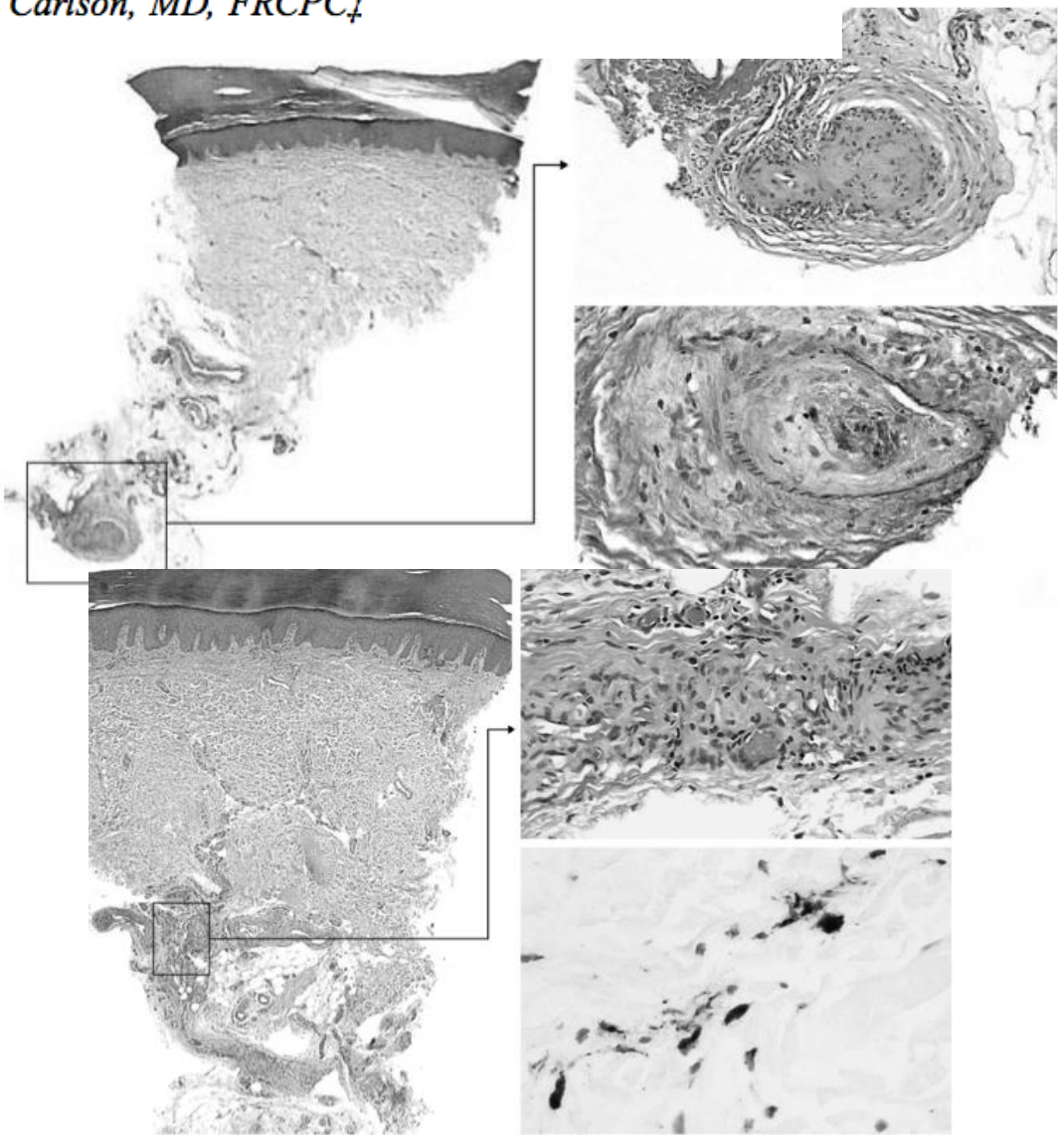
Saleh and Mutasim. J Cutan Pathol 2009; 36: 1269-

''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‡*







Am J Dermatopathol. 2008; 30: 145-9

''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

Am J Dermatopathol. 2008; 30: 145-9

Paraneoplastic vasculitis

Cutaneous Lymphocytic Vasculopathy in Lymphoproliferative Disorders—A Paraneoplastic Lymphocytic Vasculitis of the Skin

NICHOLAS A. PAVLIDIS,[1] GEORGE KLOUVAS,[1] MARIA TSOKOS,[2] MARIA BAI,[3] and HARALAMPOS M. MOUTSOPOULOS[1]

- 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

Pavlidis et al. Leukemia and Lymphoma. 1995; 16:477-82

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)

Pavlidis et al. Leukemia and Lymphoma. 1995; 16:477-82

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

Pavlidis et al. Leukemia and Lymphoma. 1995; 16:477-82

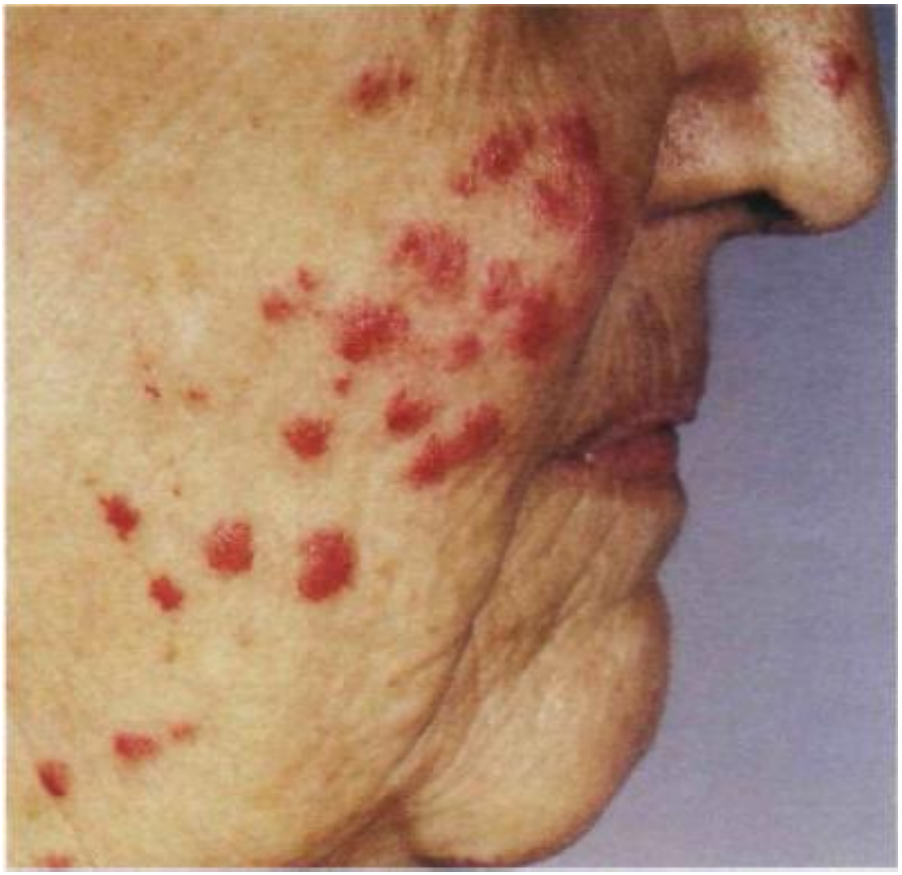
British Journal of Dermatology 1996; **135**: 471–474.

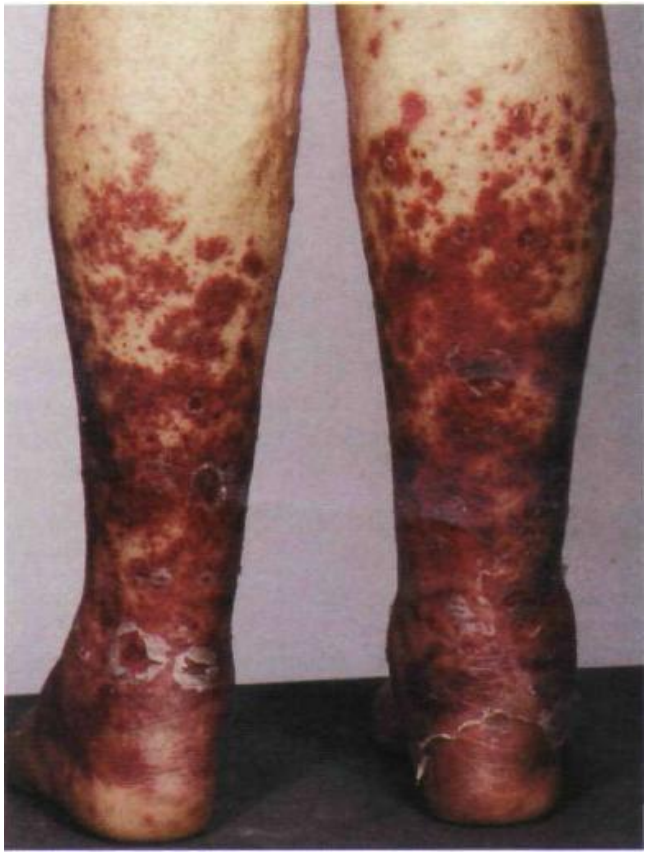
Cutaneous lymphocytic vasculitis in acute myeloid leukaemia

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.*

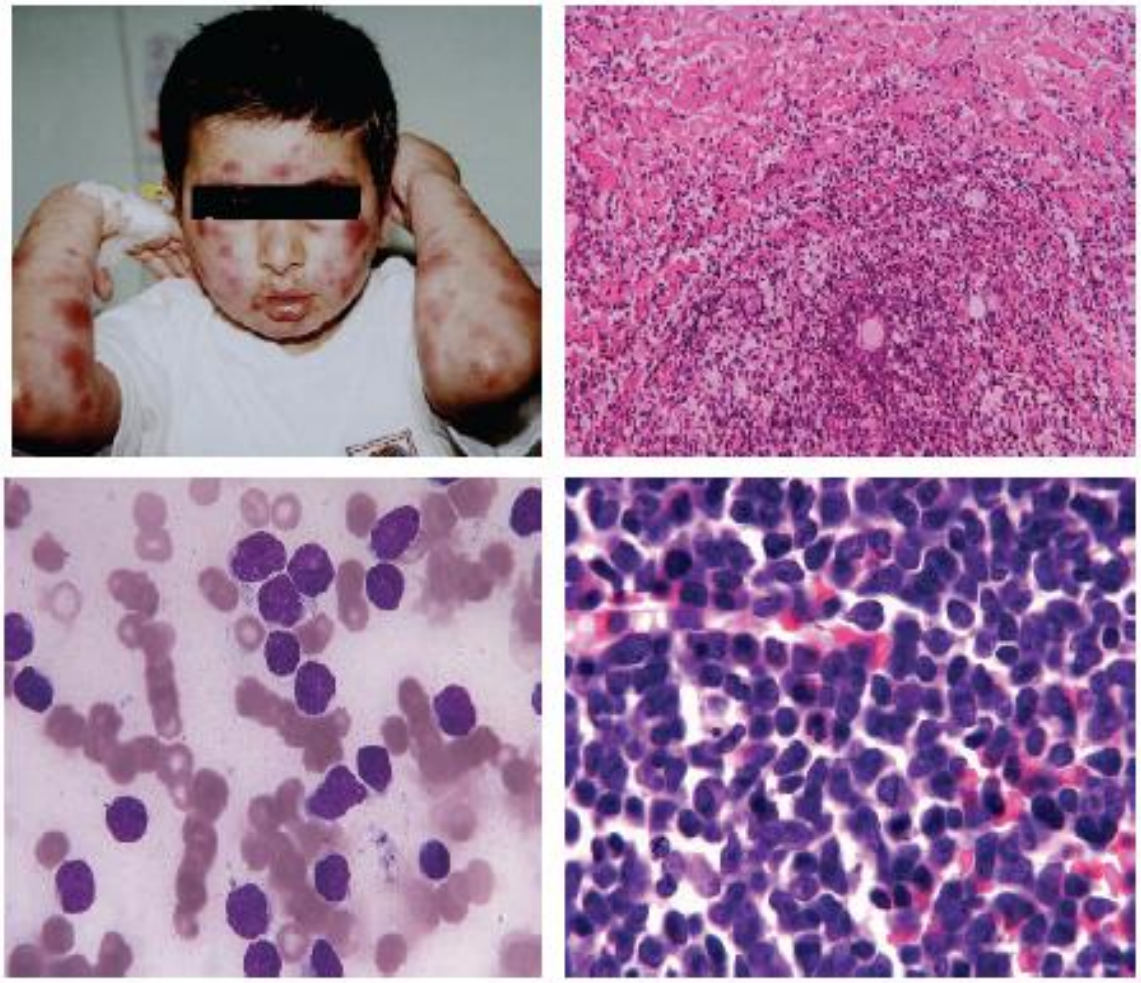
Accepted for publication 2 November 1995





bjh images in haematology

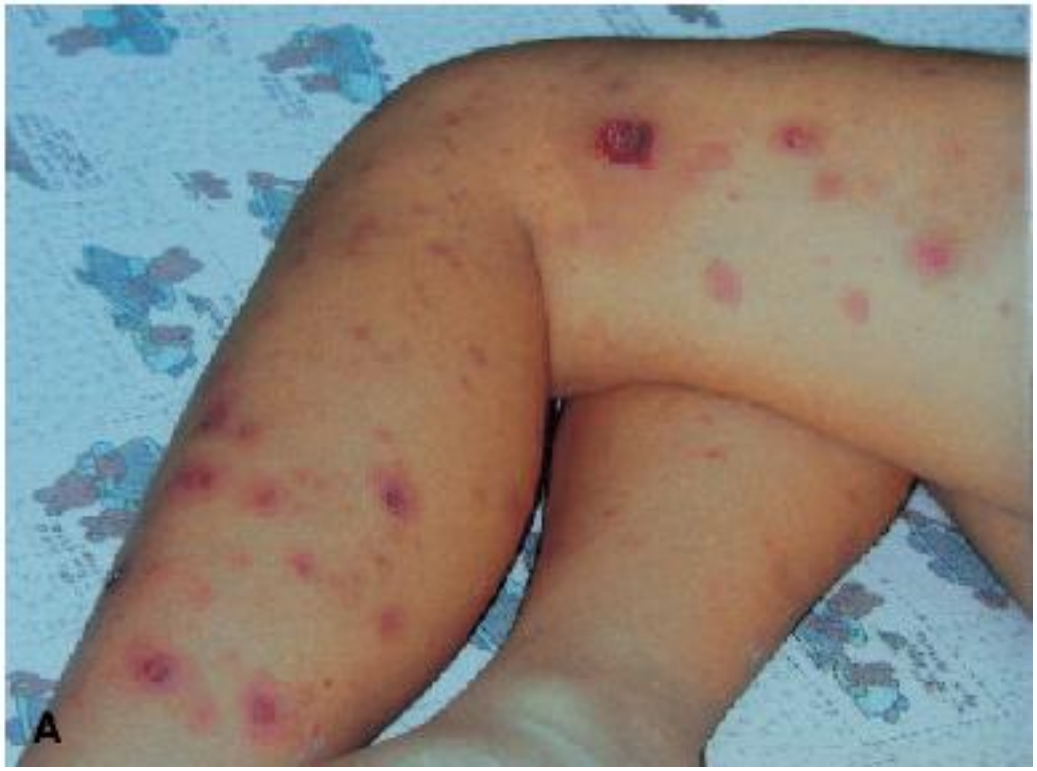
Acute lymphoblastic leukaemia presenting as vasculitis



Gupta A et al. BJH 2005; 132:384

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.



Jaing T, et al. J Ped Hematol/Oncol 2002; 24(7):555-7

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 leukocytoclasia 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