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Focus of the Presentation

- Unusual Vasculopathies
- Nutritional Insufficiencies
Histological patterns of Vascular injury

- Vasculitis
- Thrombotic Vasculopathy
- Other
56 year old female with pigmented purpura on the legs
Lekocytoclastic Vasculitis

**Associated conditions**
- Hypersensitivity (including drug)
- Collagen vascular disease (RA, SLE, MCTD, Sjögrens)
- Cryoglobulinemia type II and III
- Henoch-Schonlein purpura
- Infection
- ANCA-associated vasculitis
- Behcet’s
- Malignancy
- r/o infectious etiology

**Circulating immune complexes Type 3 Hypersensitivity reaction**

**Palpable purpura**
- Blisters
- Ulcers
- Nodules
- Urticaria

**Histology**
- Superficial and mid dermal vessels or capillaries
- Fibrinoid necrosis
- Red cell extravasation
- Vasculocentric neutrophilic/eosinophilic infiltrate
- Leukocytoclasia
Challenges in diagnosis of leukocytoclastic vasculitis

- Recognition of early LCV and urticarial vasculitis
Urticarial Vasculitis

Clinical Associations
- Hypocomplementemic
  - Collagen vascular disease (RA, SLE, MCTD, Sjögrens)
  - Idiopathic urticarial vasculitis syndrome
- Normocomplementemic
  - Allergic
  - Henoch-Schonlein purpura

Histology
- ↑C1q antibody
- Systemic disease

Circulating immune complexes Type 3 Hypersensitivity reaction

Persistent urticaria with fixed lesions
- LCV
  - LCV/Neutrophilic Urticaria
  - Can lack fibrinoid necrosis (anectodal)
  - Can involve capillaries (anecdotal)
Drug-induced vasculitis associated with positive ANCA

- Hydralazine
- Propythiouracil
  - also penicillamine, allopurinol, sulfasalazine, carbimazole, minocycline, phenytoin and cefotaxime
- p-ANCA, with propylthiouracil with increased serum anti-myeloperoxidase antibodies
- Erythema evolving into purpura, atypical distribution (face, ear lobes)
- Can be severe with renal (pauci-immune necrotizing glomerulonephritis) and pulmonary (alveolar hemorrhage) involvement
- Symptoms regress after discontinuation of the drug, but elevated ANCA levels may persist for a long time
45 yo. F

Recent onset of a rapidly progressing painful violaceous rash on both breasts which developed week after initiation of Warfarin treatment
Thrombotic vasculopathy

Hypercoaguable state
- DIC
- Protein S/S
- Purpura fulminans
- Warfarin necrosis
- Factor V Laden
- Prothrombin
- Antithrombin III

Endothelial injury
- Lupus anticoagulant
- Anticardiolipin
- Degos
- TTP
- HUS
- Homocystinuria

Other
- Emboli
- Cryo type I
Warfarin-induced skin necrosis

- 3-5 days following initiation of therapy
- Imbalance in Vitamin K-sensitive coagulation factors due to different half-lives
- Protein C and S deficiency
- INR can be normal

Anticoagulation

↓ II, VII, IX, X

↓ Protein C/S

Thrombosis
LCV

Vasculitis

Subcutaneous thrombotic vasculopathy

Cholesterol emboli

Calciphylaxis
Warfarin-induced skin necrosis is a rare complication of anticoagulant therapy with a high associated morbidity and mortality requiring immediate drug cessation. Cutaneous findings include petechiae that progress to ecchymoses and hemorrhagic bullae. Characteristic dermatopathological findings are diffuse dermal microthrombi with endothelial cell damage and red cell extravasation with progression to full-thickness coagulative necrosis. The lesions of warfarin-induced skin necrosis may be difficult to differentiate from mimickers, but skin biopsy in conjunction with careful consideration of the clinical history, including time of onset, cutaneous distribution of the lesions, and laboratory findings, are essential for prompt diagnosis and patient treatment. Herein, we review the clinical and histologic features helpful for differentiating warfarin-induced skin necrosis and report a case illustrative of the diagnostic difficulty that may at times be encountered in clinical practice. (J Am Acad Dermatol 2009;61:325-32.)

**Key words:** anticoagulant; coumarin; warfarin; hypercoagulable; protein C; therapeutic complication; thrombosis; thrombotic vasculopathy; warfarin-induced skin necrosis.

Click to download:  
http://dermnetnz.org/reactions/warfarin-necrosis.html
A 61 year-old executive
Macular lesions and livido reticularis on lower extremities and arms. Hx of Bell's palsy and "orbital fibroinflammatory tumor". Mild ↑ IgG with no other significant findings.
Macular arteritis

Clinical
- Asymptomatic
- Pigmented erythematous macules
- Livido racemosa

Histology
- Medium-size vessel lymphocytic vasculitis
- Subcutaneous tissue
- Rare eos, histiocytes
- Endovascular hyalinizing fibrin ring
- Thrombangitis obliterans

DDx
- Cunaneous PAN
- Thrombophlebitis

No systemic involvement
- Associated conditions
Cutaneous arteritis presenting with hyperpigmented macules: Macular arteritis

Howard Fein, MD, Anita P. Sheth, MD, and Diya F. Mutasim, MD
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 2005;519-22.)

Fig 1. Multiple hyperpigmented, linear to whirled macules and patches on lower extremity of patient 1.

and plasma cells. An elastic tissue stain demonstrated a continuous elastica that confirmed the arterial nature of the affected vessel.

Extensive laboratory evaluation was performed and the results are shown in Table I. The lesions have remained asymptomatic without progression for 18 months of observation; no treatments have
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

Arch Dermatol. 2008;144(9):1175-1182
81 year old F with 7-year history of polycythemia vera with recent onset of exquisitely-painful ulcers of her right calf
Hyalinizing vasculopathy:
• Atrophie blanche
• Hydorxyurea-induced ulcer
• Non-specific finding
Hydroxyurea-induced ulcer

Hydroxyurea:
1st line treatment for Ph- Chronic Myeloproliferative Neoplasms (PV, Thrombocytemia, CML)

Ulcers:
• 2-5% of patients
• Dose and time-dependent
• M=F
• Lower leg, lateral malleolus, pretibia>>Feet and hands
• Also mucosal lesions

Histology:
Poorly described in the literature

Personal experience (2 cases):
Hyalinizing vasculopathy reminiscent of Atrophie blanche
Recurrence of Hydroxyurea-induced Leg Ulcer After Discontinuation of Treatment

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[Image: Microscopic and clinical images of leg ulcer with labeled structures]
59-year-old Caucasian man with type II diabetes mellitus, hypercholesterolemia and hypertension
Collagen IV
Cutaneous collagenous vasculopathy with generalized telangiectasia: an immunohistochemical and ultrastructural study

We report a 54-year-old male, with a 3-year history of spreading asymptomatic generalized cutaneous telangiectases. The patient had no mucosal or nail involvement, no positive family history and no clinical evidence of systemic disease or bleeding diathesis. Histologically, the superficial small dermal blood vessels were dilated and showed thickened walls with hyaline perivascular material, staining as collagen. The vessel walls were PAS and colloidal iron stain positive, and immuno-histochemically lacked actin staining. Collagen IV, fibronectin and laminin antibodies showed the material deposited around the basement membrane zone. Ultrastructurally, the vessels were post-capillary venules (PCV) and showed marked collagen deposition around the basal lamina. There were many abnormally banded widely spaced fibres with 100-150 nm periodicity (Luse bodies), in addition to regular banded collagen. Pericytes were sparse and lacked intracytoplasmic filaments, and few vein or fibroblastic cells were seen embedded within the collagen. We believe this is a form of cutaneous microangiopathy not previously described, with distinct morphology and unique ultrastructural features. It may be due to a genetic defect with erroneous production of disorganized collagen in the cutaneous microvasculature. Dermatologists and Dermatopathologists should be aware of this unusual cutaneous vasculopathy.


Samih Salama and Donald Rosenthal
Departments of Pathology and Dermatology, St. Joseph’s Hospital and McMaster University, Hamilton, Ontario, Canada

We report a 54-year-old male, with a 3-year history of spreading asymptomatic generalized cutaneous telangiectases. The patient had no mucosal or nail involvement, no positive family history and no clinical evidence of systemic disease or bleeding diathesis. Histologically, the superficial small dermal blood vessels were dilated and showed thickened walls with hyaline perivascular material, staining as collagen. The vessel walls were PAS and colloidal iron stain positive, and immuno-histochemically lacked actin staining. Collagen IV, fibronectin and laminin antibodies showed the material deposited around the basement membrane zone. Ultrastructurally, the vessels were post-capillary venules (PCV) and showed marked collagen deposition around the basal lamina. There were many abnormally banded widely spaced fibres with 100-150 nm periodicity (Luse bodies), in addition to regular banded collagen. Pericytes were sparse and lacked intracytoplasmic filaments, and few vein or fibroblastic cells were seen embedded within the collagen. We believe this is a form of cutaneous microangiopathy not previously described, with distinct morphology and unique ultrastructural features. It may be due to a genetic defect with erroneous production of disorganized collagen in the cutaneous microvasculature. Dermatologists and Dermatopathologists should be aware of this unusual cutaneous vasculopathy.


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Case vignette 12:

57 year-old Hispanic female
“Firm, painful nodules and plaques on the legs and lower abdomen with overlying retiform purpura and progressing into painful ulcers over the period of weeks”
Biopsy was performed to r/o calciphylaxis
Case 1: Clinical information

- Morbid obesity
- Diabetes mellitus (40 years)
- End-stage renal disease requiring hemodialysis
- Hypertension
- Not on coumadin
Case 2 (85 yo F): Clinical information

- Morbid obesity
- Pulmonary hypertension
- Atrial fibrillation
- CHF
- C. diff. colitis
- On coumadin
Case 2 (72 yo M): Clinical information

- Obesity
- Ischemic cardiomyopathy
- CHF
- Diabetes mellitus
- Myocardial infarction
- Atrial fibrillation
- Arterial hypertension,
- End-stage renal disease (an dialysis)
CPAS
Subcutaneous thrombotic vasculopathy syndrome

Severe medical conditions

Normal Ca x PO₄

Obesity
Human calciphylaxis

Ischemic skin necrosis
Vascular calcifications in SQ
Chronic renal failure (hemodialysis)

1960’s
↑ Ca x PO$_4$

2010’s
Ca x PO$_4$

CRF (hemodialysis)
↑PTH, ↑Vit D

Female sex
Obesity
Corticosteroid use
↑Al
Hypercoagulable state

DM
Liver disease
Heart disease
Autoimmune
Inflammatory
Calciphylaxis: pathophysiology:

Calcification

Vascular injury  Thrombosis
Calciphylaxis: pathophysiology:

- Calcification of vascular blood vessels is critically regulated by osteoprotegerin/receptor activator of nuclear factor-κB (NF-κB)/and its ligand (RANKL) system which regulates activation of NF-κB, the key final common pathway of cellular responses to injury (such as free radicals), chronic inflammation (cytokines) and infectious agents.

- In the bone, NF-κB activation results in decreased mineralization but in blood vessels it results in osteoblastic transformation of vascular smooth muscle and vascular calcifications.

Diagram:
- ↑ Calcification
- RANKL
- OPG
- Vascular injury
- Thrombosis
- NF-κB
Subcutaneous thrombotic vasculopathy in calciphylaxis:

- 73% (11/15 cases)
  - 100% (7 of 7) with Ca x PO$_4$ < 60 mg$^2$/dL$^2$
  - 40% (2 of 5) with Ca x PO$_4$ > 60 mg$^2$/dL$^2$
Subcutaneous Thrombotic Vasculopathy

Calciphylaxis

$\text{Ca} \times \text{PO}_4$
Subcutaneous Thrombotic Vasculopathy Syndrome: An Ominous Condition Reminiscent of Calciphylaxis: Calciphylaxis Sine Calcifications?

Artur Zembowicz, MD, PhD,*† Paula Navarro, MD,*‡ Stephanie Walters,*§
Stephen R. Lyle, MD, PhD,†§ Samuel L. Moschella, MD,|| and Danielle Miller, MD||

Abstract: Ischemic skin necrosis can be a cause of severe morbidity and mortality. It can be due to a number of systemic conditions such as (1) thrombotic vasculopathy syndromes, (2) calciphylaxis, (3) septic or cholesterol emboli, and (4) cutaneous vasculitis. We present 3 patients with a clinicopathological syndrome consisting of ischemic skin necrosis associated with histological pattern of subcutaneous thrombotic vasculopathy-extensive microvascular thrombosis confined to small vessels and capillaries of the subcutaneous tissue. All 3 patients were obese and had severe pre-existing medical conditions. Skin biopsies showed intravascular thrombosis involving small arterioles and capillaries of the subcutaneous tissue. Distribution of vascular involvement by thrombotic process was similar to that observed in calciphylaxis, but calcifications were not observed. Two patients died within 3 months of diagnosis. One patient died 2 years after the presentation. Review of 15 biopsies of calciphylaxis revealed areas of subcutaneous thrombotic vasculopathy in 11 cases (73%). Our study shows that subcutaneous thrombotic vasculopathy syndrome is a potentially lethal condition showing overlapping features between thrombotic vasculopathy syndromes and calciphylaxis. Clinicopathological analysis suggests that it may be a rare variant of calciphylaxis sine calcifications or an early prodromal stage of calciphylaxis. This conclusion is in keeping with increasing appreciation of importance of thrombosis and vascular injury in calciphylaxis.

Key Words: calciphylaxis, thrombotic vasculopathy, skin ulcer

(Am J Dermatopathol 2011;33:796–802)
Nutritional Deficiencies
53 year old female with a history of strokes. The patient had been on total parenteral nutrition for 2 years. Developed a recalcitrant skin rash involving the face, groin and hands for the past several months prior to biopsy.
Diagnosis

- Acquired acrodermatitis enteropathica/Multifactorial nutritional deficiency
Nutritional Deficiencies

Histological Patterns

- Pure Zn deficiency
- Multifactorial
- Vitamin C deficiency
Nutritional Deficiencies

- World wide: protein, calorie, vitamin deficiencies
- Western world:
  - Genetic/metabolic
    - Acrodermatitis enteropathica
    - Rare metabolic genodermatoses
  - Acquired nutritional deficiency dermatoses:
    - Acquired Zn deficiency (rarely pure)
    - Necrolytic migratory erythema syndromes
    - Vitamin C deficiency (scurvy)
    - Rare selective vitamin deficiencies
Acrodermatitis Enteropathica

- Acrodermatitis enteropathica:
  - AR
  - Impaired transport of Zn from the intestines
  - SLC39A4 encodes zinc transporter Zip4
  - 1 per 500,000 children
- Negative zinc balance
Acrodermatitis Enteropathica
Key Clinical Features

- Onset after weaning from the breast
- Scaly or bullous
- Acral dermatitis (scalp, periorificial, genital areas, hands and feet)
Age 6.9 years (foot)

Case 32-2008 — A 10-Year-Old Girl with Recurrent Oral Lesions and Cutaneous Bullae

James G.H. Dinulos, M.D., and Artur Zembowicz, M.D.
Age 10.8 years
Diagnosis

Acrodermatitis enteropathica

Zinc level 311 (nl 670 to 1240 (μg/L))
Bullous lesions in acrodermatitis enteropathica delaying diagnosis of zinc deficiency: a report of two cases and review of the literature

Acrodermatitis enteropathica (AE) is a rare disorder associated with poor absorption of zinc. A variety of clinical and histological findings have been reported in the literature, described mainly in isolated cases.

Sarah L. Jensen¹, Catherine McCuaig², Artur Zembowicz³,⁴,⁵ and Mark A. Hurt⁶
1 y/o WF with blistering eruption
Necrolytic acantholysis with reticulated pseudospongiosis
Zn supplementation

Before

After

Photos courtesy of Albert Yan, M.D.
Acquired Zinc Deficiency

- Intestinal malabsorption syndromes
- Extensive burns
- Crohn disease
- Sickle cell anemia
- Celiac sprue
- Systemic malignancies
- Pancreatic insufficiency
- Renal tubular dysfunction

- Defect of mammary zinc secretion
- Short bowel syndrome
- Diets high in phytates
- Total parenteral nutrition
- Prematurity
Case vignette 27:

• 61 yo M
• Weight loss
• Sore tongue and generalized rash
• Nocturia
Necrolytic Migratory Erythema (Glucagonoma Syndrome)

- Paraneoplastic syndrome
- Glucagon-producing (α-cell) pancreatic islet tumor
- Often MEN1
- Hypercatabolic state
  - ↓ Zn
  - ↓ free fatty acids
  - ↓ amino acids
  - ↓ vitamins B
  - ↓ essential nutrients
A. Carcinoid Syndrome  
B. Pemphigus vulgaris  
C. Paraneoplastic pemphigus  
D. Linear IgA Disease  
E. Necrolytic Migratory Erythema
Necrolytic Migratory Erythema

- Erythema, epidermal necrosis, bullae, shedding and hyperpigmentation
- Diabetes mellitus
- Weight loss
- Anemia (B\textsubscript{12})
- Stomatitis, cheilitis, glossitis (B\textsubscript{2}, B\textsubscript{3})
- Diarrhoea (B\textsubscript{3})
Necrolytic Migratory Erythema (Glucagonoma syndrome) 
Histological features

- Acanthosis
- Parakeratosis
- Epidermal pallor
- Epidermal cell vacuolization
- Later: superficial and intraepidermal mixed infiltrate with lymphocytes, eosinophils and neutrophils
- Residual: post-inflammatoty hyperpigmentation
Necrolytic Migratory Erythema Syndromes

- Necrolytic migratory erythema (glucagonoma syndrome)
- Paraglucagonoma
- Necrolytic aral erythema
Paraglucagonoma syndrome

- Other pancreatic and non pancreatic cancers
- Chronic pancreatitis
- Celiac disease
- Jejunal adenocarcinoma
- Crohn’s disease
- Hepatic cirrhosis
Necrolytic Acral Erythema

Abdallah et. al. Journal of the American Academy of Dermatology
Volume 53, Issue 2, August 2005, Pages 247-251

Steve Brady, Northeast Dermatology, Portsmouth, HN
Nutritional Deficiency Histological Patterns

Pure Zn

Multifactorial
61 year-old male presented unconscious to the emergency room with hemorrhagic rash on lower extremities. The biopsy was performed to rule out vasculitis.
Scurvy

- Cofactor for prolyl hydroxylase
- Weak collagen
- Alcoholics and inadequate intake of fruits
- Twisted hair, perifollicular hemorrhage, purpura