Vasculitis and the Dermatologist: General approach, pitfalls, and pearls

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Vasculitis—Definition

• Inflammation and destruction of blood vessels resulting in tissue damage

• Diagnosis depends on characteristic clinical findings and histology → clinical-pathologic correlation

• Clinical morphology correlates with the size of the affected blood vessels such that disorders are classified according to vessel size
## Vasculitis Classification

<table>
<thead>
<tr>
<th>Affected Vessels</th>
<th>Classification</th>
<th>Subclassification</th>
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**Vasculitis Classification:**
The size of involved vessels is predictive

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Using the skin exam alone, we can narrow the differential diagnosis considerably
Vasculitis Classification:
The size of involved vessels is predictive

**Small Vessels**
- Skin:
  - Palpable purpura, urticarial papules, vesicles, petechiae
- Kidney:
  - Glomerulonephritis
- Nerves:
  - Not typically involved

**Medium Vessels**
- Skin:
  - Livedo reticularis, retiform purpura, ulcers, sub-q nodules, digital necrosis
- Kidney:
  - Arterial aneurysms and renovascular hypertension
- Nerves:
  - Wrist or foot drop (mononeuritis multiplex)
Regardless of the terminology used, these lesions are a symptom rather than a disease entity in and of themselves.

In other words, to diagnose skin-limited vasculitis, one must first rule out systemic manifestations (renal, joint, GI) and underlying conditions that affect management and prognosis.

Patients may also start with skin-limited disease and develop other manifestations over time, necessitating close follow-up.

I use the term “small vessel vasculitis of the skin” initially.
In the case of palpable purpura:

- The small vessel involvement accounts for the small size of the lesions
- Complement cascade and inflammation account for palpability and symptomatology
- RBC extravasation results in nonblanching purpura
- The effect of gravity on immune complex deposition accounts for lesion distribution

Think small vessel vasculitis or overlap conditions which can affect small vessels
Small Vessel Vasculitis—Presentation

- Absent are manifestations more typical of medium vessel vasculitis:
  - Subcutaneous nodules
  - Livedo reticularis
  - Retiform purpura
  - Larger hemorrhagic bullae
  - More significant ulceration and necrosis

- If such lesions are seen, suspect medium vessel vasculitis or vasculitis overlapping small and medium vessels:
  - Cutaneous or systemic polyarteritis nodosa
  - ANCA-associated vasculitis
  - Cryoglobulinemic vasculitis

If there is both palpable purpura and medium vessel manifestations, suspect ANCA or Cryo vasculitis
Small Vessel Vasculitis—Work-Up

When a patient presents with lesions suspicious for vasculitis, initial work-up should try to answer three basic questions:

1) Are the lesions due to vasculitis?

2) Are other organ systems involved?

3) Are there findings which help establish a particular diagnosis?
Small Vessel Vasculitis—Work-Up

The diagnosis of vasculitis can be confirmed by biopsy showing leukocytoclasia and fibrinoid necrosis of small vessels

- A well-established but not old lesion (1-2 days) should be biopsied; lesions are dynamic—timing and location are critical
- Tissue eosinophilia may suggest drug-induced vasculitis
- Depth or severity of inflammation may predict systemic involvement or even underlying malignancy

Direct immunofluorescence should be performed (fresh lesion)

- IgA vasculitis is a special category (Henoch-Schonlein purpura) with more frequent renal, GI, and joint involvement
- IgM may correlate with renal involvement, or cryoglobulinemia
- C3 or IgG at the DEJ (lupus band test) may suggest hypocomplementemic urticarial vasculitis and underlying SLE

Small Vessel Vasculitis—Work-Up

• Biopsy should be performed whenever possible; even the most astute clinician can be fooled by mimickers of vasculitis
  – Beware path reports that have leukocytoclasia or perivascular neutrophils but not fibrinoid necrosis; read the fine print
  – Beware mimickers with secondary vasculitis (bug bites, ulcers, trauma, neutrophilic dermatosis, etc.)

• Clinical-pathologic correlation is key
Small Vessel Vasculitis—Differential

Differential Diagnosis of Purpuric Macules and Papules:

- Skin-limited small vessel vasculitis
- IgA vasculitis
- Cryoglobulinemic vasculitis
- ANCA-associated vasculitis
- Arthropod bites
- Macular purpura due to trauma, skin fragility, or anticoagulation
- Platelet dysfunction or deficiency
- Pigmented purpuric dermatosis
- Cholesteral emboli
- Septic emboli
- Livedoid vasculopathy
Small Vessel Vasculitis—Work-Up

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1) Are the lesions due to vasculitis?

2) Are other organ systems involved?

3) Are there findings which help establish a particular diagnosis?
Small Vessel Vasculitis—Work-Up

• A thorough ROS and physical exam should be performed, along with basic labs and those dictated by history / exam

• Vasculitis may be confined to the skin, but systemic vasculitis and underlying disease states / triggers must be excluded
Small Vessel Vasculitis—Etiologies

ETIOLOGIES OF CUTANEOUS SMALL VESSEL VASCULITIS

- Infection (15–20%)
- Autoimmune connective tissue disease (15–20%)
- Drug (10–15%)
- Neoplasm (5%)
- Idiopathic (45–55%)
Small Vessel Vasculitis—Etiologies

- Antibiotics, particularly β-lactams, are common culprits, but almost any drug or additive can cause vasculitis.

- Upper respiratory infections, group A Strep, and Hepatitis C are common causes, but numerous infectious triggers are reported.

- Determining a specific cause can be difficult.

Small Vessel Vasculitis—Etiologies

Vasculitis can also be a presenting sign of connective tissue disease, most often lupus or Sjogren syndrome

Such cases may be associated with more significant internal involvement

Small Vessel Vasculitis—Work-Up

A careful history and review of systems is essential for separating patients with skin-limited vasculitis from those with more significant systemic involvement or underlying disease.
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Work-up</th>
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<tbody>
<tr>
<td>Constitutional</td>
<td>Fever, chills, sweats, weight loss, fatigue</td>
<td>Fever</td>
<td>CBC, ESR, CRP, ANA</td>
</tr>
<tr>
<td>HEENT</td>
<td>Hair loss, dry eyes/mouth, eye pain, oral/nasal ulcers, sinusitis, epistaxis</td>
<td>Iritis, sinus tenderness, otitis, lymphadenopathy</td>
<td>ANCA, ophtho exam, laryngoscopy</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>CP, orthopnea, PND</td>
<td>Gallop, rub, edema</td>
<td>ECG, echo</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>SOB, cough, hemoptysis, wheeze</td>
<td>Crackles, wheeze, rhonchi</td>
<td>CXR</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abd pain, melena, N/V</td>
<td>Abd tenderness, hepatosplenomegaly</td>
<td>Fecal occult blood, LFTs</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Joint pains, muscle aches</td>
<td>Joint swelling</td>
<td>X-ray, ultrasound</td>
</tr>
<tr>
<td>Renal</td>
<td>Hematuria, frothy urine</td>
<td>Hypertension, lower extremity edema</td>
<td>BMP, UA, urine sediment, UProt/Cr</td>
</tr>
<tr>
<td>Neuro</td>
<td>Paresthesias, numbness, weakness</td>
<td>Foot/wrist drop, reflexes, sensation, proprioception</td>
<td>Nerve conduction studies</td>
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</table>
In most cases of small vessel vasculitis of the skin, significant systemic manifestations are unlikely.

Arthralgias are fairly common during flares, but frank synovitis or arthritis is rare and suggests systemic disease.

Other symptoms (e.g. constitutional, neurological, pulmonary) are red flags for other types of systemic vasculitis.

If one or more of these symptoms is present, a targeted workup should proceed to identify potentially severe extracutaneous manifestations.
Small Vessel Vasculitis—Work-Up

No standard protocol for this workup exists (data emerging), but it should be guided by clinical signs and symptoms.

Most episodes are skin-limited and resolve within 3-4 weeks.

– Not every test need be ordered in every patient.
– Avoid ordering unnecessary tests, as false positive or irrelevant results can be confusing.

However, serious internal organ dysfunction does rarely occur.
Most common “trap”

Ordering too little (e.g. ignore systemic symptoms or fail to order urinalysis)

Ordering too much (e.g. low-positive ANA or APLA that should never have been ordered)
Small Vessel Vasculitis—Work-Up

• When the presentation is straightforward and ROS negative, nothing more than a CBC, BMP, and UA (with micro) may be required.

• Of these tests, the urinalysis is most essential; the presence of glomerulonephritis is most likely to change management.
Small Vessel Vasculitis—Work-Up

• Additional indiscriminate work-up is unlikely to be helpful

• Review of biopsy-proven small vessel vasculitis cases:
  – ESR/CRP are rarely normal (<10%) and therefore rarely helpful
  – ANCA and SPEP rarely abnormal (<5%); order only when indicated
  – Screening radiographs (CXR, CT, angio) essentially never positive
Small Vessel Vasculitis—Work-Up

• But additional work-up is indicated when there is concern for systemic involvement or other types of vasculitis
  – Fecal occult blood test in those with abdominal pain or GI bleed
  – A chest x-ray or chest CT if cough or dyspnea
  – Any other organ-specific targeted workup should proceed based on review of systems and examination

• By definition, if skin lesions suggestive of med or small-to-medium vessel vasculitis are present (e.g. retiform purpura), appropriate work-up for those conditions (e.g. cryo, AAV, PAN) should ensue
Small Vessel Vasculitis—Work-Up

• For those with concerning symptoms or chronic / recurrent lesions with no obvious cause, reasonable workup includes:
  – CBC, BMP, urinalysis, and LFTs
  – Infectious serologies, including hepatitis B and C, HIV, antistreptolysin-O
  – Rheumatologic workup, including ANA and RF (which screens for rheumatoid arthritis and is a surrogate for mixed cryoglobulins)

• Second-level tests include:
  – SPEP / immunofixation to look for evidence of a paraprotein
  – C3 and C4 levels, which may be low in urticarial vasculitis or systemic lupus and signal more significant systemic involvement
  – ANCA's, which are strongly suggestive of ANCA-assoc vasculitis
  – Cryoglobulins
Summary:

• Straightforward case, negative ROS: CBC, BMP, UA w/micro, +/- CXR and fecal occult blood

• Unclear trigger, other symptoms: above labs plus HBV, HCV, HIV, ASO, ANA, RF

• Second level tests: C3/C4, ANCA, Cryos, SPEP

• Any other work-up warranted by presenting signs / symptoms
• Initial therapy (and prognosis) are dictated by the work-up:
  – More aggressive systemic therapy is necessary in the case of renal or other organ involvement
  – Treat / address underlying condition
If systemic involvement has been excluded, the treatment of skin-limited vasculitis should be symptom-focused.

Because most cases are minimally symptomatic and self-limited, aggressive immunosuppression is generally not advisable (I rarely use prednisone for skin-only disease):

- Rest and elevation
- Compression stockings
- Topical steroids for itch relief
Small Vessel Vasculitis—Management

• Systemic therapy is indicated if severe, intractable, or recurrent (8-10% become chronic)
  – For discomfort, ulceration, and psychosocial impact
  – For any episode that is not self-limited and lasts longer than a few weeks, even if relatively asymptomatic

• Unfortunately, there is a dearth of high-quality data:
  – Only one small RCT, for colchicine
  – All else is case reports and expert opinion (dapsone, azathioprine, others)
  – Adequate dose and duration of therapy are likely important

• Complete resolution or cure of chronic small vessel vasculitis may be elusive, but chronic systemic glucocorticoids usually not indicated
A Randomized Multicenter Study for Isolated Skin Vasculitis (ARAMIS)

Colchicine, dapsone, azathioprine

ARAMIS
A Randomized Multicenter Study for Isolated Skin Vasculitis
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IgA Vasculitis (Henoch-Schonlein Purpura)

Most common in children

- Viral URI or Strep pharyngitis often precede onset by 1-2w
- Overall, 40% due to infection
- Drug trigger in around 20%

Consider paraneoplasia in adults (90% male)

IgA Vasculitis—Management

• Management depends on severity of cutaneous and systemic symptoms, employing the same agents (colchicine, dapsone)

• Cochrane review showed no benefit of early steroids at the time of diagnosis for preventing renal complications of IgA vasculitis:
  – Prophylactic steroids are not recommended
  – They do ameliorate joint and abdominal pain and accelerate resolution of renal symptoms, if they develop

IgA Vasculitis—Prognosis

• Prognosis is favorable but depends on severity of renal disease; lasts up to 6 months in 1/3 of cases

• Persistent nephropathy occurs in 8%, progressive renal failure in 1-3%
  – 31% of adult patients experience renal insufficiency during the course of disease

• Those with hematuria or proteinuria should be carefully followed

How do you treat/prevent and monitor for renal involvement in Henoch Schönlein Purpura (IgA vasculitis)?

- Frequent UA w/ micro and BP monitoring for at least 6 months; renal involvement usually develops within 1 month
- No benefit to prophylactic steroids, but are indicated if renal complications develop

Urticarial Vasculitis

As many as 5-10% of chronic urticaria patients

“Red flags”:
- Lesions last >24 hours (not evanescent)
- Burn rather than itch
- Resolve with bruise-like marks
- Systemic symptoms like fever, arthralgias
- Lack of response to antihistamines

Courtesy of Dr. Misha Rosenbach
Urticarial Vasculitis

“Red flags” should prompt a biopsy → small vessel vasculitis

Work-UP:
ROS and physical exam
Basic labs, UA, etc.
C3 and C4 levels
Normocomplimentemic Urticarial Vasculitis

Patients with normal compliment levels:

Skin-limited and self-resolving

Best considered a subset of cutaneous small-vessel vasculitis
Hypocomplimentemic Urticarial Vasculitis

Patients with low C3 and C4 complement levels:

Much more likely to have:

- Systemic lupus (>50%)
- Arthritis (50%)
- Obstructive pulmonary disease (20%)
- GI symptoms (20%)
- Glomerulonephritis

Hypocomplimentemic urticarial vasculitis syndrome (HUVS)
Cryoglobulinemic Vasculitis (small/medium)

- Cryoglobulins: cold-precipitable circulating immunoglobulins
- Can cause vasculopathy (vascular occlusion) or vasculitis (vascular inflammation)
# Cryoglobulinemic Vasculitis (small/medium)

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<th>Composition</th>
<th>Association</th>
<th>Pathophys</th>
<th>Manifestations</th>
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<tr>
<td>I</td>
<td>Monoclonal IgM or IgG</td>
<td>Lymphoprolif. disorders</td>
<td>Vascular occlusion / vasculopathy</td>
<td>Raynaud’s, retiform purpura, gangrene, acrocyanosis</td>
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<td>II</td>
<td>Monoclonal IgM against Polyclonal IgG</td>
<td>HCV, HIV, HBV, autoimmune disease, also lymphoprolif. disorders</td>
<td>Vasculitis</td>
<td>Palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis</td>
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*Mixed cryos (Type II and III) are antibodies which bind to the Fc (crystallizable) region of other antibodies; this is referred to as “rheumatoid factor activity”*
Cryoglobulinemic Vasculitis

Rheumatoid factor (RF) is the poor man’s cryos (+ in >70%)

Cryoglobulins often falsely negative

Draw during flare, keep warm, transport immediately, repeat if negative

Complement levels usually low (90%)

Check HCV, HIV, HBV, SPEP
Cryoglobulinemic Vasculitis (small/medium)

- Underlying infectious or autoimmune process causes B-cell stimulation and expansion, essential to disease pathogenesis

- Most common disease association is hepatitis C (70-90%)
  - Half of HCV patients have circulating cryos; 15% develop symptoms

- Cryoglobulin-antibody immune complexes form and deposit in vessel walls, activating complement

Skin, joints, and nerves most frequently involved:
- Hallmark is a mixed small and medium vessel vasculitis with a predilection for dependent and cold-exposed sites
Mixed small and medium vessel manifestations
--palpable purpura
--retiform purpura
--livedo reticularis
--cold-induced acrocyanosis
Questions

What lab test is a good screening tool for cryo vasculitis?

- Rheumatoid factor (RF)
- Positive in almost all patients and usually highly elevated
The ANCA-associated vasculitides...

- Granulomatosis with polyangiitis (GPA), formerly Wegener’s
- Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss
- Micoscopic polyangiitis (MPA)

...have overlapping features, characteristically the pulmonary-renal syndrome of pulmonary hemorrhage and necrotizing glomerulonephritis
ANCA-Associated Vasculitis (small/medium)

• With the advent of ANCA testing, these diseases can be diagnosed with 85% sensitivity and 98% specificity

• But, ANCA testing can also be a source of confusion; it is worth reviewing the interpretation of this test
ANCA Testing

• Patient serum is incubated on a slide with ethanol-fixed human neutrophils

• Binding is measured using indirect immunofluorescence, and the staining pattern is noted by the technician
ANCA Testing

The two major IF patterns associated with vasculitis are:

- C-ANCA, in which staining is diffuse throughout the cytoplasm
- P-ANCA, in which staining is perinuclear

A third, “atypical” pattern may be seen; can be confused with P-ANCA
ANCA Testing

A number of limitations:

• Subjective nature of visual interpretation of the IF pattern
• Lack of standardization and reference for normal range
• Staining patterns can be seen in other conditions besides vasculitis

(sensitive but not specific)
ANCA Testing

C-ANCA:

Relatively specific for GPA and MPA

P-ANCA:

Can be seen in EGPA, MPA
Inflammatory rheumatic disease (e.g. SLE, RA), IBD, CF, anti-GBM, and drug-induced vasculitis

Atypical ANCA:

Suspect drug, IBD, rheumatic disease, other

Both C-ANCA and P-ANCA:

Suspect drug-induced vasculitis
For these reasons, positive immunofluorescence is confirmed by ELISA; these antibodies are what is really relevant in vasculitis:

- **C-ANCA** → PR3 (proteinase 3) antibodies
- **P-ANCA** → MPO (myeloperoxidase) antibodies

ELISA is less sensitive, but more specific, higher positive predictive value.

Both antigens are located in the granules of neutrophils.

Antibodies to other antigens account for non-MPO, non-PR3 ANCAs, atypical ANCAs.
ANCA Testing

- The optimal approach to testing is therefore to screen for ANCA with IIF and confirm positive results using PR3 and MPO ELISA.

- When ANCAs are ordered, the lab should report back both IIF and ELISA reflexively; a positive ANCA is incomplete without ELISA results.
ANCAs are most useful when confirmed with ELISA, appropriate clinical features, and histology, in which case they are sensitive and specific.
Granulomatosis with Polyangiitis

AKA Wegener’s

Initial presentation (90%): rhinorrhea, severe sinusitis, etc.
Granulomatosis with Polyangiitis

Cough, dyspnea, and chest pain:
Pulmonary infiltrates (70%)

Glomerulonephritis (85%)

Cutaneous findings (50%):
Palpable purpura
Ulcers
Subcutaneous nodules (extensor surfaces)

→ Mix of small and med vessel manifestations
Churg-Strauss nodules / PNGD

Central necrosis is typical
Eosinophilic Granulomatosis with Polyangiitis

AKA Churg-Strauss

1) Allergic rhinitis, nasal polyps, adult-onset asthma

2) After several years, fever and peripheral eosinophilia develop
   Eosinophilic pneumonia and gastroenteritis

3) Granulomatous vasculitis of the skin, nerves, lungs, heart, liver, spleen, kidneys, intestines

50% are ANCA negative
When positive, 75% are P-ANCA / MPO
• How do you interpret positive ANCA results?

- ANCA is merely an operator-dependent immunofluorescence test.
- Positive C or P-ANCA must be confirmed by ELISA to be specific for vasculitis.
- Discordant results suggest other causes of ANCA positivity, such as drug-induced vasculitis or IBD, should be considered.
Question

• Does a negative ANCA exclude ANCA-associated vasculitis?

- 30% of MPA patients and 50% of EGPA patients are ANCA negative
- Up to 10% of GPA patients (particularly those with limited disease) may have negative ANCA
- ANCA status may change over time
Case Example

- The finding of medium vessel vasculitis suggests polyarteritis nodosa

- The patient’s fever, malaise, myalgias, abdominal symptoms, and hypertension are concerning for systemic PAN
Case Example

• Laboratory work-up:
  – CBC and CMP unremarkable
  – HBV, HCV, HIV negative
  – ANCA negative
  – ESR 16, CRP <0.5
  – Urinalysis w/ 2-5 RBCs
Case Example

• What work-up would you get next?

• CT Angiogram (Abd/Pelvis):
  – Subtle vascular changes: mild narrowing of proximal common hepatic and proximal splenic artery; mild dilation of the distal splenic artery; mild dilation of the distal bilateral common iliac arteries; focal mild narrowing in the proximal left common iliac

- Imaging (angiography) showing aneurysmal dilation and narrowing of vessels can be crucial to the diagnosis of PAN
- Patient begun on systemic steroids
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Medium Vessel Vasculitis (Polyarteritis Nodosa)

• Medium-sized arteries and veins

• Systemic symptoms include:
  – Fever and weight loss (90%)
  – Arthralgia / arthritis (75%)
  – Peripheral neuritis (75%) with foot drop
  – Renal involvement (50%) with hypertension
  – GI involvement (40%) with abdominal pain, bleeding
  – Stroke, myocardial infarction, intestinal infarction
  – Spares the lungs
Polyarteritis Nodosa

• Skin lesions are seen in 60% of patients with systemic PAN → medium vessel manifestations
  – Retiform purpura
  – Ulcers
  – Digital necrosis
  – Livedo reticularis
  – 5-10mm subcutaneous nodules distributed along blood vessels

• Biopsies be deep enough to sample medium vessels in the subcutis
Polyarteritis Nodosa

Fibrinoid necrosis of medium-sized vessels, thrombus, neutrophils

Multiple microaneurysms on angiogram

Questions

What are the characteristic renal manifestations of polyarteritis nodosa?

- Hypertension from renal artery aneurysms
- A lack of hematuria on urinalysis does not rule out renal PAN
Questions

How does “benign” cutaneous PAN differ from systemic PAN?

- Characteristic skin lesions (livedo, nodules, ulcers), but no significant systemic manifestations
- Systemic renal, GI, and cardiac complications can develop over time, even >10 years later (very rare)
Summary

- Use the physical exam, clinical acumen to your advantage
- Always confirm vasculitis with biopsy; clin-path correlation is key
- Don’t over-order labs in straightforward cases of small vessel vasculitis
- Let review of systems and exam guide systemic work-up
- Urinalysis with micro is of paramount importance
- Monitor UA and blood pressure periodically while active rash, especially (and frequently) in IgA vasculitis
Learn to use selected laboratory tests when they are indicated

- Low C3 and C4 signify a worse prognosis in urticarial vasculitis
- RF is a good screening tool for cryo vasculitis (poor man’s cryos)
- ANCA results must be confirmed with PR3 and MPO ELISA; they are just one piece of the diagnostic puzzle
- Evaluate for systemic PAN with a CT-angiogram; renal involvement manifests with hypertension, not hematuria

Disease severity must guide management

Vasculitis can be difficult, but a systematic clinical and diagnostic approach leads to successful diagnosis and management
A Randomized Multicenter Study for Isolated Skin Vasculitis (ARAMIS)

Colchicine, dapsone, azathioprine

ARAMIS
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Multi-center observational study to evaluate histopathology and transcriptome of cutaneous lesions in idiopathic vasculitis

- Describe systematically the histopathology of cutaneous vasculitis
- Perform gene expression profiling on lesional skin to define novel pathways to aid classification and targeted therapies

Clinical Transcriptomics in Systemic Vasculitis (CUTIS)

Vasculitis Clinical Research Consortium (VCRC)

Peter Grayson, MD, MSc, Robert Micheletti, MD, Peter Merkel MD, MPH
The Dermatology Foundation has supported & advanced my career.
Thank you

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