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; thus, disorders are classified according to vessel size
## Vasculitis Classification

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Vasculitis Classification:
The size of involved vessels is predictive

**Small Vessels**
- **Skin:**
  - Palpable purpura, urticarial papules, vesicles, petechiae
- **Kidney:**
  - Glomerulonephritis
- **Lungs:**
  - Alveolar capillaritis, hemorrhage, pulmonary infiltrates

**Medium Vessels**
- **Skin:**
  - Livedo reticularis, retiform purpura, ulcers, sub-q nodules, digital necrosis
- **Kidney:**
  - Arterial aneurysms and renovascular hypertension
- **Lungs:**
  - Nodules, cavitation
Small Vessel Vasculitis—Terminology

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.
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

• Biopsy should be performed whenever possible; even the most astute clinician can be fooled by mimickers of vasculitis
  – Beware path reports that have leukocytoclasis 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—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 VASCUULITIS

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

• 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 the presence of systemic disease

• 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; 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

• 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 might 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, which are strongly suggestive of ANCA-associated vasculitis
  – Cryoglobulins
Small Vessel Vasculitis—Work-Up

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
Small Vessel Vasculitis—Management

• 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
Small Vessel Vasculitis—Management

• 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
  – 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
IgA Vasculitis

Initial presentation often indistinguishable from other small vessel vasculitis

Abdominal pain, bleeding (65%), arthralgia/arthritis (63%)

IgA-associated glomerulonephritis (40%)
IgA Vasculitis—Prognosis

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

• Persistent nephropathy occurs in 8%, progressive renal failure in 1-3%; those with hematuria or proteinuria should be carefully followed

Questions

How do you treat/prevent and monitor for renal involvement in Henoch Schonlein 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
Normocomplimentemic Urticarial Vasculitis

Patients with normal complement 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)
Questions

When making the diagnosis of urticarial vasculitis, what test has the greatest prognostic value?

- Complement levels (C3 and C4)
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
Questions

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

- Rheumatoid factor (RF)
- Positive in almost all patients and usually highly elevated
ANCA Testing

- The optimal approach to testing is 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
ANCA Testing

ANCAs are most useful when confirmed with ELISA, appropriate clinical features, and histology, in which case they are sensitive and specific.
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 medium vessel manifestations
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
Question

• 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
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

Courtesy of Dr. Misha Rosenbach

Courtesy of Dr. Antoine Sreih
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
Thorough ROS, PE

**SMALL**

- Macular or palpable purpura, urticarial lesions

  - Punch biopsy, DIF
  - Thorough ROS, PE

  - UA, BMP, CBC; +/- FOBT, CXR, ANA, RF, ANCA, C3, C4, HBV, HCV, HIV, cryos
  - Work-up dictated by ROS/PE

**MEDIUM**

- Livedo reticularis, nodules, ulcers, infarctions

  - Large punch to fat or excisional biopsy
  - Thorough ROS, PE

  - UA, BMP, CBC; ANCA, HBV, HCV, HIV, RF, cryos, CT-A
  - Work-up dictated by ROS/PE

- RF+, cryos, +/- HCV: CryoVas
  - Rhinitis, granulomas, C-ANCA: GPA
  - No rhinitis, gran., P/C-ANCA: MPA
  - Asthma, eos, +/- P-ANCA: EGPA

- Skin only, DIF not IgA: CSVV
- DIF IgA: IgA vasculitis (HSP)
- Urticarial, low C3, C4: HUVS

- Med vessel, ANCA neg, systemic sx’s: PAN
  - No systemic sx’s: cutaneous PAN
Summary

- 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
Summary

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

Vasculitis can be difficult, but a systematic clinical and diagnostic approach leads to successful diagnosis and management
Thank you

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