Vasculitis pitfalls and pearls

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY:

I have no relevant relationships with industry to disclose
Objectives

1) Use clinical cases to illustrate real-life dilemmas encountered during the evaluation of vasculitis

2) Review a basic approach to diagnosis and management of vasculitis presenting in the skin

3) Condense the lessons learned into key “pitfalls” and “pearls” to remember
Case Example

86yo patient admitted with GI bleed, new lung cancer

Consulted for palpable purpura on the lower legs

- What work-up should be performed to confirm the diagnosis and investigate potential systemic manifestations and underlying triggers?
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 there findings which help establish a particular diagnosis?

3) Are other organ systems involved?
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

Small Vessel Vasculitis—Work-Up

Direct immunofluorescence should be performed (fresh lesion)

- IgA vasculitis (Henoch-Schonlein purpura) is a special category with more frequent renal, GI, and joint involvement

Palpable purpura in 86yo patient with GI bleed, new lung cancer

Biopsy shows small vessel vasculitis

DIF shows perivascular IgA

= IgA Vasculitis
(aka Henoch-Schonlein purpura)
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 there findings which help establish a particular diagnosis?

3) Are other organ systems involved?
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
IgA Vasculitis

The initial presentation of IgA vasculitis may be indistinguishable from LCV / CSVV...

- Abdominal pain, bleeding (65%), arthralgia/arthritis (63%)
- IgA-associated glomerulonephritis (40%)

UA w/ micro shows 50-100 RBCs
Glomerulonephritis
(small vessel vasculitis of the kidney)

Any significant or persistent hematuria or proteinuria must be investigated.

Urinalysis with micro is the single most important initial lab to order in the setting of vasculitis.
IgA Vasculitis

Initial presentation often indistinguishable from other small vessel vasculitis

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

IgA-associated glomerulonephritis (40%)

UA w/ micro shows 50-100 RBCs

➢ Not followed up / urine sediment not examined
IgA Vasculitis

Given 10mg daily prednisone from rheumatology for his skin

Presents after 1 month to dermatology clinic

Skin is clear, but repeat UA shows packed RBCs

UProt/Cr ratio = 10; Cr = 2

Arranged urgent evaluation by nephrology, diagnosed with glomerulonephritis
IgA Vasculitis (Henoch-Schonlein Purpura)

Most common in children

- Viral URI or Strep pharyngitis often precede onset by 1-2 weeks
- 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 (colchicine, dapsone commonly used for skin-limited disease)

- Cochrane review, RCT, and large series do not show benefit of early steroids at diagnosis for preventing renal complications of IgA vasculitis:
  - Prophylactic steroids are not recommended
  - Steroids are an effective and reasonable first-line therapy for joint, GI, and renal symptoms, if they develop

Arthritis Rheumatol. 2017 Sep;69(9):1862-1870.
Usual therapy for IgA nephropathy / vasculitis:

- ACE inhibitor or ARB if > 0.5g/day proteinuria
- If > 0.75-1.0g/day, or if rise in Cr, consider renal biopsy and initiate steroid taper, usually 6 months
- Mycophenolate usually added as a steroid-sparing agent if there is persistent proteinuria and evidence of active inflammation after that

➢ Close monitoring of UA, BMP, and BP
IgA Vasculitis—Prognosis

• Overall 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%, 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 monitor for and prevent / treat 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 they are indicated if renal complications develop

Pitfalls and Pearls—IgA vasculitis

1) Pitfall:
   - Failing to check for (or follow up on) hematuria and proteinuria as part of the evaluation of vasculitis \(\rightarrow\) this is one complication which may not cause symptoms (at first)

1) Pearl:
   - Recognize the importance of the urinalysis for assessing patients with vasculitis (in particular IgA vasculitis), and ensure abnormal findings are fully investigated
   - Check urinalysis and blood pressure at diagnosis and frequently thereafter, especially in the first 1-6 months
2) Pitfall:

- Assuming the primary medical team “knows better”

2) Pearl:

- Don’t be afraid to help guide medical management when appropriate
3) **Pitfall:**
- Thinking of IgA vasculitis / HSP as a “childhood-only” disease

3) **Pearl:**
- IgA vasculitis is not that rare in adults
- Consider special circumstances, like screening for cancer in older male patients presenting with IgA vasculitis
Case Example

66yo woman with 3 months of tender subcutaneous nodules on the arms and legs

Also reports fever, myalgias, malaise, and vague abdominal symptoms (queasiness, anorexia)

BP elevated to 158/88 x 2
Case Example

What diagnoses are you considering?

What would you do to establish the diagnosis and screen for associated systemic complications?
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

• Are we satisfied? Reassured?
• What additional work-up is indicated?
Medium vessel vasculitis of the kidney results in renovascular hypertension.

Absence of hematuria / proteinuria on urinalysis does not rule out renal involvement in PAN.
Case Example

• What is the test of choice to evaluate for visceral involvement in PAN?

➢ CT Angiogram (Abd/Pelvis):
  • Narrowing of proximal common hepatic and proximal splenic artery; dilation of the distal splenic artery, distal bilateral common iliac arteries, proximal left common iliac

➢ Angiography showing aneurysmal dilation and narrowing of vessels can be crucial to the diagnosis of systemic PAN

➢ Patient begun on high-dose prednisone
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
Polyarteritis Nodosa

Biopsies be deep enough to sample medium vessels in the subcutis

*Courtesy of Dr. Antoine Sreih*
Polyarteritis Nodosa

Fibrinoid necrosis of medium-sized vessels, thrombus, neutrophils

Multiple microaneurysms on angiogram

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
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)
- While the prognosis is better than in systemic PAN, chronic and relapsing symptoms are common
Factors associated with relapse and need for escalation of immunosuppression:

- Cutaneous ulceration
- Higher CRP level
- Higher ANC level
1) Pitfall:
   - Being falsely reassured by a urinalysis without hematuria / proteinuria

1) Pearl:
   - Renal PAN presents with hypertension, not necessarily hematuria and proteinuria
2) Pitfall:
   - Being falsely reassured by a generally unremarkable review of systems

2) Pearl:
   - Patients with systemic PAN will develop systemic manifestations, but initial symptoms can be subtle
   - Have a low threshold for ordering a CT-angiogram to help screen for systemic vasculitis in those you diagnose with cutaneous lesions of PAN
3) Pitfall:
   - Under-treating or over-treating skin-limited disease

3) Pearl:
   - Medications like dapsone and colchicine can be effective for cutaneous PAN
   - But ulcerative disease may require more aggressive therapy (e.g., prednisone, methotrexate, azathioprine)
61yo man with a recent MRSA infection, treated with vancomycin

Presented to the ED with palpable purpura about 7 days after starting vancomycin
Skin biopsy demonstrates small vessel vasculitis

DIF negative for IgA

Exam and review of systems otherwise not concerning (no joint, GI, or other symptoms)
Case Example

Basic labs, including CBC, CMP, UA w/ micro, unremarkable

ESR 46
ANA 1:160

dsDNA, anti-Sm, anti-SSA/B, C3, C4 all negative / normal
Case Example

• What is the diagnosis?

• What should we do with the elevated ESR and low-titer ANA?

• How do we work up cutaneous small vessel vasculitis / leukocytoclastic vasculitis appropriately?
• 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

• For an initial episode, 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
Red Cell Cast and Dysmorphic RBCs

Courtesy of Dr. Amar Bansal
## Symptoms/Signs of Systemic Vasculitis

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Work-up</th>
</tr>
</thead>
<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, congestion, oral/nasal ulcers, 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>
</tr>
</tbody>
</table>
• Additional indiscriminate work-up is unlikely to be helpful

• Review of biopsy-proven small vessel vasculitis cases evaluated at Harvard and Penn:
  – 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) rarely positive (~5%), only 18.5% sensitive
• 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
  – ANCAss, which are strongly suggestive of ANCA-assoc 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
Case Example

What is the diagnosis?

What to do with the elevated ESR and low-titer ANA?

How do we work up cutaneous small vessel vasculitis appropriately?
There are no real red flags here on exam or ROS

Basic labs, including UA, are unremarkable

Diagnosis of skin-limited small vessel vasculitis fits best
We understand the ESR and ANA add little in this context.

Absent other findings of lupus or systemic disease, we’ll file this away for now unless new symptoms emerge.
Most likely trigger instead is the vancomycin, versus Staph

Without significant systemic or cutaneous symptoms, no systemic therapy is required

Lesions resolve over 3-6 weeks
1) Pitfall:
   ➢ Ordering unnecessary labs because you think you’re supposed to, then being stuck interpreting the (unhelpful) results

1) Pearl:
   ➢ Don’t over-order labs in straightforward cases of small vessel vasculitis on the skin
   ➢ Instead, let the review of systems and exam guide the systemic work-up
2) Pitfall:
   - Putting too much stock in acute phase reactants and other tests of questionable value (e.g., low-titer ANA, APLAs)

2) Pearl:
   - Acute phase reactants (ESR and CRP) are frequently elevated in skin-limited vasculitis and, conversely, can be normal in systemic vasculitis
   - Reserve “second-level tests” and imaging for when they are indicated and when looking for something specific
Case Example

• 67-year-old woman
• 4 months of:
  – Rhinitis
  – Fatigue
  – Fevers
  – Weight loss
• 1 week dyspnea
• 1 week of rash on extremities
Case Example

• What further work-up is indicated?
  – Creatinine 2
  – Urinalysis: +RBC casts
  – CT – ground glass opacities
  – ANCA negative

• What is the diagnosis?
Biopsy shows small and medium vessel necrotizing vasculitis with scattered extravascular granulomas

Courtesy of Dr. Campbell Stewart
Case Example

• What further work-up is required?
  – Creatinine 2
  – Urinalysis: +RBC casts
  – CT – ground glass opacities
  – ANCA negative

• What is the diagnosis?
  ➢ “Pulmonary-renal syndrome” of granulomatosis with polyangiitis
  ➢ Treated with pulse-dose steroids and rituximab
Case Example

46yo man with asthma and allergic rhinitis, peripheral eosinophilia

Presented with severe urticaria

P-ANCA negative

Developed mononeuritis multiplex shortly thereafter

This kind of nonspecific cutaneous presentation is not unusual for EGPA

50% are ANCA negative
When positive, 75% are P-ANCA / MPO
ANCA-Associated Vasculitis (small/medium)

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

➢ A brief note about ANCA testing...
ANCA Testing

• The ANCA test is an indirect immunofluorescence study

• A positive result (C- or P-ANCA) can be seen in other diseases and should be confirmed with the ELISA (PR3 and MPO, respectively), which is more specific for vasculitis

C-ANCA / PR-3  P-ANCA / MPO  Atypical ANCA
ANCA Testing

- The result of this testing is just one piece of the diagnostic puzzle

- Need complementary data (clinical features, histology) to make a diagnosis
ANCA Testing

- ANCA testing and ELISA do not have to be positive to make a diagnosis of ANCA-associated vasculitis
  - 30% of MPA patients and 50% of EGPA patients are ANCA neg
  - Up to 10% of GPA patients may have negative ANCA
  - ANCA status may change over time
Pitfalls and Pearls—ANCA-associated vasculitis

1) Pitfall:
   - Being overly dependent on the result of ANCA testing (or any lab result) in making a diagnosis of vasculitis

1) Pearl:
   - ANCA results (positive or negative) are just one piece of the diagnostic puzzle
   - Interpret in the context of other complementary data (ELISA, clinical features, histology)
   - A negative test does not rule out ANCA vasculitis
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.

Evaluate for systemic PAN with a CT-angiogram; renal involvement manifests with hypertension, not hematuria.

ANCA results must be confirmed with PR3 and MPO ELISA; they are just one piece of the diagnostic puzzle.

Disease severity must guide management.
A Randomized Multicenter Study for Isolated Skin Vasculitis (ARAMIS)

Colchicine, dapsone, azathioprine

ARAMIS
A Randomized Multicenter Study for Isolated Skin Vasculitis
A VCRC Pilot Project
VCRC - 5562

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Clinical Transcriptomics in Systemic Vasculitis (CUTIS)

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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