Annual Rheumatology & Therapeutics Review for Organizations & Societies
Update on Granulomatosis with Polyangiitis (Wegener’s)

Philip Seo, MD, MHS
Director, Johns Hopkins Vasculitis Center
Director, Johns Hopkins Rheumatology Fellowship
Johns Hopkins University School of Medicine
Baltimore, MD
Objectives

• Discuss the evaluation of Henoch-Schönlein Purpura (IgA Vasculitis), and other forms of cutaneous vasculitis
• Review the differential diagnosis for cutaneous polyarteritis nodosa
• Discuss the presentation and management of urticarial vasculitis
References

• Jachiet M et al. Arthritis Rheumatol 2015; 67: 527
• Loricera J et al. Medicine (Baltimore) 2014; 93:53
• Ozen S et al. Ann rheum Dis 2010; 69: 798
• Audemard-Verger A. Autoimmun Rev 2015; 14: 579
• Criado PR. Autoimmun Rev 2016; 15: 558
IgA Vasculitis
(Henoch-Schönlein Purpura)

Neglected Vasculitis
Vignette

• 20 year old man with an unremarkable past medical history until December, when he developed a headache.

• The next day, he developed a rash, which he described as flat, red lesions on his legs.

• These lasted for a few weeks, and then resolved with some hyperpigmentation.

• He continued to have monthly episodes, associated with rash on his arms, legs, feet, hands, and buttocks.

• Urinalysis demonstrates hematuria (30 RBC/PF) and proteinuria (+1)

• He occasionally has episodes of severe abdominal pain, which are so severe that they make him miss school
**Mandatory**: Purpura or petechiae, not related to thrombocytopenia, with lower limb predominance, and at least one of the four following criteria:

- Arthritis/arthralgia
- Renal Involvement (hematuria and/or proteinuria)
- Abdominal pain
- Histopathology: leukocytoclastic vasculitis or glomerulonephritis with IgA predominance
## IgA Vasculitis ≠ IgA Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>IgA Nephropathy</th>
<th>IgA Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-renal symptoms</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Age at onset</td>
<td>15-30 years</td>
<td>&lt;15 years</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Risk of renal failure</td>
<td>15%/10 years</td>
<td>15%/10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(highest with nephrotic proteinuria)</td>
</tr>
</tbody>
</table>
Biopsies: a (Very) Brief Primer

• H&E: Is there evidence of blood vessel inflammation?
  • Yes!: Fibrinoid necrosis, degranulation, diapedesis
  • Meh: Perivascular cuffing (consistent with “early vasculitis”)

• DIF: What is the process driving the vasculitis?
  • Full house deposition pattern: lupus
  • Pauci-immune: ANCA-associated vasculitis (GPA/MPA/EGPA)
  • IgM/C3: Cryoglobulinemic vasculitis (et al.)
  • IgA: IgA Vasculitis
IgA Vasculitis and IgA Nephropathy: Secondary Forms

**IgA Nephropathy**
- Alcoholic cirrhosis
- Celiac Disease
- Crohn’s disease
- Chronic infection
- Malignancy
- Lymphoproliferative disorders
- Ankylosing spondylitis

**IgA Vasculitis**
- Drugs (ciprofloxacin, aspirin, vancomycin, ACE-I, carbidopa/levodopa, carbamazepine)
- Infection (C. diff, VZV)
- Cocaine
- IgA monoclonal gammopathy
- Alcoholic cirrhosis
- ANCA-associated vasculitis
<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>48 years</td>
<td>7.5 years</td>
<td></td>
</tr>
<tr>
<td>Age (Range)</td>
<td>21-83</td>
<td>1-20</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>56.2%</td>
<td>57.1%</td>
<td></td>
</tr>
<tr>
<td>Upper Extremity Involvement</td>
<td>41.7%</td>
<td>19.3%</td>
<td>0.004</td>
</tr>
<tr>
<td>Joint Involvement</td>
<td>27.1%</td>
<td>55.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20%</td>
<td>1%</td>
<td>0.004</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>15.8%</td>
<td>0%</td>
<td>0.026</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>79.2%</td>
<td>30.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent hematuria/proteinuria</td>
<td>58.3%</td>
<td>29.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>Complete renal recovery</td>
<td>41.7%</td>
<td>70.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Outcome

- dialysis or severely impaired renal function
- moderately impaired renal function
- nephrotic proteinuria
- minimal or moderate proteinuria
- remission

IgA Vasculitis: Treatment

• **Colitis:** Short courses of steroids
  • Prednisone, up to 1 mg/kg/d
  • Taper for 1 month

• **Glomerulonephritis**
  • Data does not demonstrate lasting benefit associated with cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine
  • There may be short-term benefit from steroids, which may not change long-term outcomes (Cochrane Report 2015)
  • Rituximab?

• **Purpura**
  • Dapsone 25 mg-100 mg/d (Check for G6PD; beware of hemolysis!)
Cutaneous Vasculitis: Other Interventions

• Cutaneous vasculitis tends to manifest in the lower extremities because of pressure and trauma
• Anything that increases circulation or trauma may lead to flare
  • Alcohol
  • Exercise
• When rest/elevation is not feasible, compression stockings may help prevent flares of cutaneous disease
  • Thigh high
  • Gradually increase to 40 mm H2O pressure
• In a pinch, steroids will work transiently . . . .
IgA Vasculitis: Summary

• IgA Vasculitis is a small vessel vasculitis, mediated by IgA, which can manifest by arthritis, colitis, and nephritis
• Adults can have a more severe phenotype than children, with more widespread purpura, and increased probability of renal insufficiency and gastrointestinal hemorrhage
• Dapsone may help mitigate the rash and gastrointestinal symptoms
• Mechanical interventions may be surprisingly effective for mitigating purpura
• Nothing seems to help alter the long-term renal outcomes
Cutaneous polyarteritis nodosa

Neglected Vasculitis
Vignette

• 54 year old man with a history of obstructive sleep apnea and hypertension

• Noted small, raised purple lesions on his legs that were non-pruritic and non-tender

• The next morning, noted they increased in size, and were associated with burning pain

• Punch biopsy demonstrated vessel destruction with diapedesis and fibrin deposition

• Treated with prednisone 40 mg, but lesions began to ulcerate

• Heard that Hopkins had a vasculitis center, and came to the ED for admission
Cutaneous polyarteritis nodosa

• Skin-limited form of polyarteritis nodosa that affects the small-sized arteries (“medium vessels”) at or below the dermo-epidermal junction

• Presents with a range of manifestations:
  • Livedo racemosa
  • Cutaneous nodules
  • Erythematous plaques
  • Cutaneous ulcerations

• May be associated with B-type symptoms, but not internal organ involvement
Cutaneous polyarteritis nodosa: Vessel Size
SKIN ULCERS MISDIAGNOSED AS PYODERMA GANGRENOsum

Vascular occlusive or venous disease
- Antiphospholipid-antibody syndrome
- Livedoid vasculopathy
- Venous stasis ulceration
- Small-vessel occlusive arterial disease
- Type I cryoglobulinemia
- Klippel–Trénaunay–Weber syndrome

Vasculitis
- Wegener’s granulomatosis
- Polyarteritis nodosa
- Cryoglobulinemic (mixed) vasculitis
- Takayasu’s arteritis
- Leukocytoclastic vasculitis plus secondary infection

Cutaneous involvement of malignant process
Lymphoma
- Angiocentric T-cell lymphoma
- Anaplastic large-cell T-cell lymphoma
- Mycosis fungoides bullosa
- Unspecified lymphomas
Leukemia cutis
Langerhans’-cell histiocytosis

Primary cutaneous infection
- Deep fungal infection
  - Sporotrichosis
- Aspergillosis
- Cryptococcosis
- Zygomycosis
- Penicillium marneffei infection
- Herpes simplex virus type 2
- Cutaneous tuberculosis
- Amebiasis cutis

Drug-induced or exogenous tissue injury
- Munchausen’s syndrome or factitial disorder
- Hydroxyurea-induced ulceration
- Contact vulvitis
- Injection-drug abuse with secondary infection
- Bromoderma
- Loxoscelism (bite of a brown recluse spider)
- Drug-induced lupus

Other inflammatory disorders
- Cutaneous Crohn’s disease
- Ulcerative necrobiosis lipoidica
Is it . . . .

Primary blood vessel inflammation, with surrounding inflammatory infiltrate, \textit{OR}
  \begin{itemize}
    \item Cutaneous polyarteritis nodosa, systemic vasculitis, drug reaction
  \end{itemize}

Primary panniculitis, with incidental destruction of the blood vessel, \textit{OR}
  \begin{itemize}
    \item Infection, pyoderma gangrenosum, ulcerative erythema nodosum, malignancy, factitious
  \end{itemize}

Blood vessel occlusion, surrounded by necrotic tissue
  \begin{itemize}
    \item Hypercoagulability, hyperviscosity, livedoid vasculopathy, drug abuse
  \end{itemize}

\textit{All three patterns may be reported by the pathologist as evidence of vasculitis!}
Livedoid Vasculopathy

• Thrombotic, non-inflammatory occlusion of the medium-sized arterioles, leading to painful ulcerations of the lower extremities
• Heals with “atrophie blanche” (white scars)
• “Summer livedo”; pain out of proportion to findings
• May occur in association with SLE, APS, and other hypercoagulable states, including plasminogen activator inhibitor I 4G/4G
• Treatment: subcutaneous heparin, pressure stockings, elevation, avoidance of trauma
Lymphocytic thrombophilic arteritis

• Also known as **macular arteritis**

• Clinically presents as
  • **Asymptomatic macules**
  • **Livedo racemosa**

• Pathology:
  • Dense lymphocytic infiltrate in the small-sized arteries of the deep dermis
  • Ring of hyalinized fibrin in the lumen of the affected vessel

• Controversy: May belong on the spectrum of cutaneous PAN
Retiform purpura with ulceration
Cutaneous Polyarteritis Nodosa: Treatment

**Pharmacologic:**
- Mild: Dapsone 100 mg/d or Colchicine 0.6 mg po BID
- Moderate: Azathioprine 2 mg/kg/d or Methotrexate 25 mg/week
- Severe: Infliximab 5 mg/kg/month, IVIG, cyclophosphamide

**Non-Pharmacologic:**
- Rest/Elevation/Compression Stockings
  - Nylon stockings will help compression stockings slip over dressings
- Avoid aggressive debridement
- Wound cultures can be hard to interpret
- Skin grafting can be successful after pharmacotherapy
Non-Healing Cutaneous Ulcerations: Thoughts

• Treat the patient as if s/he had a heart attack: smoking cessation, lowering cholesterol may help improve circulation
• Check ankle-brachial index for evidence of arterial occlusive disease, which may be amenable to intervention
• Patients with arterial insufficiency may do better with lower levels of compression, with inelastic bandages
• Moisture is key; dressings using hydrocolloids, hydrogels, and calcium alginate may accelerate wound healing
• Remember that hydrocolloids can cause a contact dermatitis
• Vitamin A and pentoxifylline may also promote wound healing

J Am Acad Derm 2016; 74: 643
Cutaneous polyarteritis nodosa: Summary

- Numerous diagnoses have manifestations similar to cutaneous polyarteritis nodosa; diagnosing based on morphology is fraught
- Severe forms of this diagnosis may require wedge biopsy to reach the involved blood vessels
- Biopsy reports are particularly difficult to interpret with this diagnosis, and a careful reading of the description may be important
- Mild forms of cutaneous polyarteritis nodosa may respond to mild therapies, while severe ulcerations may require infliximab or IVIG
- Do not underestimate the importance of good wound care for healing ulcerations
Urticarial Vasculitis

Neglected Vasculitis
Vignette

• 47 year old woman presenting with a 1 year history of urticaria, starting after receiving NSAIDs for kidney stones
• Despite cessation of NSAIDs, she continued to develop raised welts on the extremities, which responded to steroids, but rapidly recurred
• She was evaluated by a dermatologist, who felt her skin lesions were classic for hives,
• Skin testing demonstrated reactions to a variety of exposures
• She was evaluated by a second dermatologist, who performed a skin biopsy, which demonstrated IgM, IgG, and C3 deposition
• She was prescribed a series of antihistamines, without relief, and has been taking almost continuous prednisone for the last 6 months
Acute Urticaria

- Transient wheals
- May be recurrent, but last less than 6 weeks
- Precipitating factors: URTI, viral infections, food/drug intolerance
- Resolve spontaneously
Chronic Urticaria (=urticaria for 6 weeks)

**Chronic inducible urticaria**
- Physical urticarial
- Cholinergic urticarial
- Contact urticaria
- Aquagenic urticarial
- Solar urticarial
- Heat-induced

**Treatment**
- Avoidance

**Chronic spontaneous urticaria**
- Rule out inducible urticaria
- Rule out chronic infection
- Stop NSAIDs

**Treatment:**
- Non-sedating antihistamines (4x)
- Steroid sparing agents: omalizumab, cyclosporine A, leukotriene antagonist, (azathioprine 2.5 mg/kg, rituximab)
- Dapsone and H2 antihistamines not recommended
- Periodic drug holidays
Chronic Urticaria Mimics: the Autoinflammatory Disorders

Cryopyrin-associated periodic syndromes
- Familial cold autoinflammatory syndrome
- Muckle-Wells syndrome
- Neonatal onset multisystem inflammatory disease (NOMID)
- Childhood onset
- Recurrent fever
- Uveitis
- Arthralgias
- Headaches

Schnitzler’s syndrome
- Adult onset
- Fever
- Musculoskeletal pain
- Lymphadenopathy
- Monoclonal gammopathy (IgM)
- Flares may occur daily to monthly
- 15% will develop Waldenstrom’s
Chronic Urticaria Mimics: the Autoinflammatory Disorders

**Chronic urticaria**
- Asymmetric
- Isolated
- Minutes
- Pruritic
- +Angioedema
- Bx: sparse infiltrate
- Acute phase reactants normal

**Autoinflammatory disorders**
- Symmetric
- Confluent
- Hours
- Burning or asymptomatic
- -Angioedema
- Bx: Dense PMN infiltrate
- Acute phase reactant elevated
- Failure to respond to antihistaminines
Urticarial Vasculitis

Chronic Urticaria

- Wheals resolve in 24 hours
- Wheals resolve without sequela
- No joint pains
- Bx: “perivascular cuffing”
- T-cell, macrophage, eosinophil
- DIF: pauci-immune

Urticarial Vasculitis

- Wheals last 1-2 days
- Wheals resolve with “bruise”
- Arthralgias/arthritis
- Bx: leukocytoclasis, necrosis
- Neutrophil
- DIF: IgG deposition
Urticarial Vasculitis

Normocomplementemic
• Primary or secondary
• May be self-limited
• 40% will resolve in 1 year
• May respond to colchicine or dapsone
• Less likely to have systemic features

Hypocomplementemic
• Secondary
  • Lupus
  • Sjogren’s syndrome
  • Malignancy
• Lesions:
  • 60% pruritic
  • 11% painful
  • 21% bruising
• Anti-C1Q
  • Systemic symptoms, glomerulonephritis, uveitis
<table>
<thead>
<tr>
<th>Organ</th>
<th>Frequency of Involvement (%)</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>100</td>
<td>Pruritic or burning wheals (lasting &gt;24 h), angioedema, bullae, lesions resembling erythema multiforme, livedo reticularis, Raynaud phenomenon, purpura</td>
</tr>
<tr>
<td>Joints</td>
<td>75</td>
<td>Arthralgias, swelling, stiffness, arthritis of single or multiple joints</td>
</tr>
<tr>
<td>Kidneys</td>
<td>60</td>
<td>Hematuria, proteinuria, decreased creatinine clearance</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>55</td>
<td>Chronic obstructive pulmonary disease, pleuritic chest pain, laryngeal edema</td>
</tr>
<tr>
<td>Eyes</td>
<td>35</td>
<td>Uveitis, episcleritis, conjunctivitis, loss of vision</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>30</td>
<td>Nausea, vomiting, diarrhea, abdominal pain</td>
</tr>
<tr>
<td>Nervous system</td>
<td>12</td>
<td>Mononeuritis, myositis, seizures, pseudotumor cerebri, increased central nervous system pressure</td>
</tr>
<tr>
<td>Cardiovascular and hematological systems</td>
<td>5</td>
<td>Raynaud syndrome, carditis, lymphadenopathy, leukopenia, thrombocytopenia, anemia</td>
</tr>
<tr>
<td>General systemic</td>
<td>10</td>
<td>Fever</td>
</tr>
</tbody>
</table>

Data from Czarnetzki BM. Urticaria. Berlin: Springer; 1986.
Urticarial Vasculitis: Treatment

• Antihistamines

• Normocomplementemic urticarial vasculitis shouldn’t require chronic therapy

• Hypocomplementemic urticarial vasculitis: pharmacotherapy
  • Azathioprine 2.5 mg/kg/d
  • Sulfasalazine 1g po BID
  • Rituximab 1 g q 6 months
  • Canakinumab 300 mg sq (JACI 2013)

• And rest/elevation/compression stockings
Urticarial Vasculitis: Summary

• Resistance to antihistamines is a good hint that the urticarial is immune-mediated
• Clinical characteristics of chronic urticarial and urticarial vasculitis may overlap
• Omalizumab may be effective for refractory chronic urticarial; rituximab may be effective for refractory urticarial vasculitis
• Normocomplementemic urticarial vasculitis may not need lifelong therapy
• In hypocomplementemic urticarial vasculitis with systemic features, look hard for evidence of SLE
Final Thoughts
Neglected Vasculitis
Neglected Vasculitis: Final Thoughts

• These rare forms of vasculitis exist on a spectrum of overlapping manifestations

• Biopsies are your friend
  • Many of these diseases look alike!

• Biopsies can also be your enemy
  • Treat the patient, not the disease