EXTRA-HEPATIC MANIFESTATIONS OF HEPATITIS C:
WHAT THE PCP NEEDS TO KNOW
OUTLINE

- Context
  - Sample cases
  - Pathophysiology and epidemiology
  - Course and treatment
- Cryoglobulinemic vasculitis
- Other EHMs by system
- Care for HCV-infected and HCV-unknown
CASE 1: MR. G

- 27yo man establishing care
- Incarceration, construction, new girlfriend
- Concerns:
  - Inattention, impulsivity
  - Back pain
  - Ankle pain
  - Hep C
CASE 1: MR. G

- **Sx**
  - No N/V, abd pain, jaundice

- **Exam**
  - Nml abd, no stigmata

- **Labs**
  - Mild transaminitis, nml CBC
  - Genotype, VL
  - Fib 4 = 0.56

- **Referred to Hepatology**
CASE 1: MR. G

*Mental health and MSK first*
CASE 1: MR. G

- New rash
  - Feet and legs
  - Itchy, hard to sleep
- “red papules and plaques, some excoriated, others violaceous”
- Punch biopsy
CASE 2: MS. S

- 56yo woman, resident transition
- Problem list:
  - MDD, GAD
  - Multiple pain complaints
  - H/o EtOH
  - Methadone maintenance
  - Chronic rhinitis
  - Hypertension
    - LVH
    - CKD2
  - HLD
  - GERD
  - Hep C
CASE 2: MS. S

- Previously referred to HMC Hepatology
- “Not bad enough to treat”
- Repeated labs and re-referred
CASE 2: MS. S

*Focus on pain, mental health, SSI*
2015:
- HTN: well-controlled
- CKD 2
CASE 2: MS. S

2016:
- Winter: Microalbuminuria 15 → 400
- Fall: Nephrotic syndrome and worsening GFR
- Referred to Neph
CASE 2: MS. S

2017:
- Renal biopsy
Complex patients
Hep C on radar, but back-burner
Role of PCP; multi-system dx
Hepatotropic and lymphotropic virus

U.S. prevalence

- 1.0% HCV RNA+
Life expectancy shorter by 15y

- Liver-related etiologies
- Risk-factors
- EHMs
1990s: interferon (IFN) and ribavirin
  - Pro-inflammatory
2011: first-generation of direct antivirals
  - Often combined
2014: second-generation of direct antivirals
**CONTEXT: HCV TREATMENT**

- EHM may
  - Be prevented
  - Remit or improve
  - Create urgency
  - Require other tx
OUTLINE

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*HCV is lymphotrophic!*
CRYOGLOBULINEMIA

Image credit Gianfranco Lauletta, DOI: 10.5772/55474
In HCV-infected persons
- 40-60% produce cryoglobulins (CG)
- 5-30% develop cryoglobulinemic vasculitis (CV)

In patients with CV
- 70 to >90% have HCV
CRYOglobulinemic Vasculitis

- Palpable purpura
CRYOGLOBULINEMIC VASCULITIS
CRYOGLOBULINEMIC VASCULITIS
CRYOglobulinemic Vasculitis
CRYOGLOBULINEMIC VASCULITIS
CRYOglobulinemic Vasculitis

Palpable purpura
Lower legs, feet, thighs, abdomen, buttocks, etc.
CRYOGLLOBULINEMIC VASCULITIS
Palpable purpura
Lower legs, feet, thighs, abdomen, buttocks, Ues
Ulceration, bullae, necrosis

CRYOGLOBULINEMIC VASCULITIS
CRYOGBLOBULINEMIC VASCULITIS

- Palpable purpura
- Fatigue, arthralgias
CRYOglobulinemic Vasculitis

- Palpable purpura
- Fatigue, arthralgias
- Nephrotic syndrome and renal failure
Type 1 membrano-proliferative glomerulonephritis (MPGN)

- Microscopic hematuria
- Proteinuria
  - Nephrotic in 20%
- Chronic renal impairment
- Acute renal failure
CRYOglobulinemic Vasculitis: Renal

*Potentially fatal, dialysis-dependent*
CRYOglobulinemic Vasculitis

- Palpable purpura
- Fatigue, arthralgias
- Nephrotic syndrome and renal failure (MPGN)
- Neurologic disease
CRYOGLOBULINEMIC VASCUITIS: PERIPHERAL NEUROPATHY

- Vasculitis of vaso nervorum
- Distal extremities
- Symmetric
- Sensory-predominant
CRYOGLOBULINEMIC VASCULITIS

- Palpable purpura
- Fatigue, arthralgias
- Nephrotic syndrome and renal failure (MPGN)
- Neurologic disease
  - Peripheral neuropathy
  - CNS vasculitis
CRYOGLOBULINEMIC VASCULITIS

- Palpable purpura
- Fatigue, arthralgias
- Nephrotic syndrome and renal failure (MPGN)
- Neurologic disease
  - Peripheral neuropathy
  - CNS vasculitis
- Raynaud’s phenomenon
CRYOglobulinemic Vasculitis

- Palpable purpura
- Fatigue, arthralgias
- Nephrotic syndrome and renal failure (MPGN)
- Neurologic disease
  - Peripheral neuropathy
  - CNS vasculitis
- Raynaud’s phenomenon
- Sicca symptoms
## CRYOGLOBULINEMIC VASCULITIS: DIAGNOSIS

- **History and clinical findings**
- **Nonspecific lab abnml**
  - hypocomplementemia
  - elevated RF
  - spurious leukocytosis or thrombocytosis
  - normocytic anemia
  - elevated ESR and CRP
- **Detection of cryoglobulins (negative in 30-40%)**
- **Tissue biopsy**
  - Skin
  - Kidney

HCV RNA (or other viral etiology)
CRYOGLOBULINEMIC VASCULITIS: APPROACH TO PATIENT

- HCV-infected patient
  - Monitor for signs and symptoms
  - Annual urinalysis and creatinine
  - Note non-specific labs
  - Low threshold to biopsy
CRYOGLOBULINEMIC VASCULITIS: APPROACH TO PATIENT

- HCV-unknown patient
  - HCV in ddx for new
    - hematuria
    - kidney injury
    - peripheral neuropathy
    - appropriate rashes
CRYOglobulinemic Vasculitis: Response to HCV Treatment

- More data for IFN than direct anti-virals
- Complete/partial remission of CV in SVR
- No improvement in CV if no SVR
Scenarios
- Acute, life-threatening
- Incomplete remission with antiviral tx

Treatments
- Rituximab
- Apheresis
- Immunosuppression
- Low-Ag diet
OUTLINE

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MPGN due to Cryoglobulinemic Vasculitis
Membranous nephropathy
Polyarteritis nodosa
+/-. Crescentic glomerulonephritis
Others: focal segmental glomerulosclerosis, proliferative glomerulonephritis, fibrillar glomerulopathy
Improved creatinine and proteinuria in SVR
Purpura due to Cryoglobulinemic Vasculitis
Purpura due to Cryoglobulinemic Vasculitis
Porphyria cutanea tarda
DERMATOLOGIC: PCT

[Image of hands showing skin lesions]
DERMATOLOGIC: PCT
DERMATOLOGIC: PCT

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DERMATOLOGIC: PCT
DERMATOLOGIC: PCT

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DERMATOLOGIC: PCT
Purpura due to Cryoglobulinemic Vasculitis

Porphyria cutanea tarda

- In HCV-infected patients:
  - up to 20% with porphyria cutanea tarda
- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda (acquired)
  - In HCV-infected patients:
    - up to 20% with porphyria cutanea tarda
  - In patients with porphyria cutanea tarda:
    - 20-85% have HCV infection
Purpura due to Cryoglobulinemic Vasculitis
Porphyria cutanea tarda
DERMATOLOGIC

- Purpura due to Cryoglobulinemic Vasculitis
- Porphyria cutanea tarda
- Lichen planus
DERMATOLOGIC

- *Purpura due to Cryoglobulinemic Vasculitis*
- *Porphyria cutanea tarda*
- *Lichen planus*
DERMATOLOGIC: LP
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- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda
- Lichen planus
DERMATOLOGIC

- **Purpura due to Cryoglobulinemic Vasculitis**
- **Porphyria cutanea tarda**
- **Lichen planus**
  - In HCV-infected patients:
    - ~5% develop LP
DERMATOLOGIC

- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda
- Lichen planus
  - In HCV-infected patients:
    - ~5% develop LP
  - In patients with lichen planus:
    - 0-60% are HCV-infected
DERMATOLOGIC

- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda
- Lichen planus
- Necrolytic acral erythema
DERMATOLOGIC

- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda
- Lichen planus
- Necrolytic acral erythema
DERMATOLOGIC:
NECROLYTIC ACRAL ERYTHEMA
Purpura due to Cryoglobulinemic Vasculitis
Porphyria cutanea tarda
Lichen planus
Necrolytic acral erythema
- In HCV-infected patients:
  - 1-2% develop NAE
- *Purpura due to Cryoglobulinemic Vasculitis*
- Porphyria cutanea tarda
- Lichen planus
- Necrolytic acral erythema
  - In HCV-infected patients:
    - 1-2% develop NAE
  - In patients with NAE
    - Nearly all HCV-infected
DERMATOLOGIC: DIAGNOSIS

- *Purpura due to Cryoglobulinemic Vasculitis*
  - Skin biopsy
- *Porphyria cutanea tarda*
  - Urine uroporphyrin levels
- *Lichen planus*
  - Skin biopsy
- *Necrolytic acral erythema*
  - Skin biopsy
HCV-infected patient
  - Monitor skin exam and have low threshold to biopsy
HCV-unknown patient
- Test for HCV in any new PCT, LP or NAE
Dermatologic: Response to Anti-Viral Treatment

- Purpura due to Cryoglobulinemic Vasculitis
  - Responds to SVR

- Porphyria cutanea tarda
  - Responds to SVR, sometimes VL suppression
  - RBV-based: new or worsening

- Lichen planus
  - Direct antivirals: theoretical benefit
  - IFN-based: new or worsening

- Necrolytic acral erythema
  - Antiviral: Limited data suggest benefit
DERMATOLOGIC: OTHER TREATMENTS

- **Purpura due to Cryoglobulinemic Vasculitis**
  - Rituximab, apheresis, immunosuppression, diet

- **Porphyria cutanea tarda**
  - Phlebotomy, antimalarial, sun protection

- **Lichen planus**
  - Immunosuppressive therapies

- **Necrolytic acral erythema**
  - Immunosuppression: Mixed data
Thyroid
- Auto-antibodies
- Dysfunction
- Papillary cancer

Diabetes mellitus type 2 and insulin resistance
RHEUMATOLOGIC

- Sjogren/sicca (*with or without Cryoglobulinemnic Vasculitis*)
  - In HCV-infected: 20-30% have sicca
  - In sicca: ~5% are HCV-infected

- Arthritis
  - In HCV-infected: ~5%
    - RA-like
    - Oligoarthritis
Peripheral neuropathy and CNS vasculitis in CV

Fatigue and deficits in concentration and working memory
HEMATOLOGIC

- Cryoglobulinemic vasculitis
- Non-B-cell lymphomas
- Monoclonal gammopathies
- Immune thrombocytopenia
- Autoimmune hemolytic anemia
- VTE?
- Ocular disorders
- Hepatic osteodystrophy
- HCV-associated osteosclerosis
- Cardiovascular disease
OTHER EHM: RESPONSE TO IFN TREATMENT

- Evidence of harm or no benefit for autoimmune-mediated
  - Thyroid, Sjogren/sicca, +/- arthritis
- Evidence of benefit in lymphoma
  - Lymphoma response in 73% overall, 83% in SVR
Benefits in preventing:
- Decreases incidence of thyroid disease or DM

Benefits in reversing:
- Some cases of improved glycemic control or improved insulin response
- Limited data suggest lymphoma response

No observed or theoretical benefit where autoimmune destruction has occurred
Usual treatments appropriate and compatible with antivirals:

- Thyroid disorders
- Diabetes mellitus
- Sjogren/sicca \((\text{with or without Cryoglobulinemic Vasculitis})\)
- Arthritis
- ASCVD risk

Lymphoma

- Increased remission with dual therapy
- Increased toxicity
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CASE 1: MR. G

- Lichen planus
- Approved anti-viral therapy
- Lost to follow up
CASE 2: MS. S

- Amyloidosis! (not an EHM)
- Other s/s of EHM
- Eventually approved anti-viral therapy
- Improved energy, mood, myalgias, engagement
EXTRA-HEPATIC MANIFESTATIONS

- Patients without HCV diagnosis
  - When to test for HCV?
- Patients with known HCV
  - Monitoring and testing
  - Response to treatments
### SUMMARY

<table>
<thead>
<tr>
<th>EHM</th>
<th>HCV unknown</th>
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<tbody>
<tr>
<td>Cryoglobulinemic vasculitis</td>
<td>Test for HCV if CV diagnosis considered</td>
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<tr>
<td>Renal disease</td>
<td>Include HCV in Ddx of new renal disease</td>
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<tr>
<td>Dermatologic conditions</td>
<td>Test for HCV if PCT, LP or NAE found</td>
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<tr>
<td>Endocrine disorders</td>
<td>Routine screening</td>
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<tr>
<td>Rheumatologic disorders</td>
<td>Routine screening</td>
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<tr>
<td>Neurologic disorders</td>
<td>Include HCV in Ddx of peripheral neuropathy (and CNS vasculitis)</td>
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<td>EHM</td>
<td>HCV known</td>
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<tr>
<td>Cryoglobulinemic vasculitis</td>
<td>Monitor Cr, urinalysis, signs and symptoms</td>
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<td></td>
<td>Low threshold to refer or biopsy</td>
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<td>EHM</td>
<td>Response to anti-viral tx</td>
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<td>Cryoglobulinemic vasculitis</td>
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<td>May also need EHM-specific therapies</td>
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<td><strong>Favorable or unknown with direct</strong></td>
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<td>Possible decrease new cases with direct</td>
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<td>Possible improvement DM with direct</td>
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<td><strong>Require EHM-specific therapy</strong></td>
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<td>Possible harm with IFN</td>
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<td>Sicca <em>too late</em>: sx tx only</td>
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<td></td>
<td><strong>Possible favorable</strong> in arthritis, but may also need EHM-specific</td>
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<tr>
<td>Neurologic disorders</td>
<td>Less studied</td>
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ACKNOWLEDGEMENTS

- Drs. Brown, Fu, Sadacharan, and Tidwell for their feedback on this presentation
- Ms. Croghan, Drs. Kowdley and Wang for their support of my hepatology elective
REFERENCES

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