A 66 year-old lady with progressive skin eruptions over bilateral lower legs for 6 years

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Brief History

• 66 year-old female
• Occupation: housewife
• Chief complaint:

Progressive skin eruptions over bilateral lower legs for 6 years
• How to describe the skin lesions of this patient?

• What else would you ask to make diagnosis?
Present Illness (1)

- Recurrent painful palpable purpura over bilateral lower legs for 6 years
- Episodic arthritis over wrists and ankles
- Numbness over bilateral plantar region
- Lower legs pitting edema
- no asthma history, no drug history
- no fever, no hemoptysis, no hematuria, no sinusitis
Present Illness (2)

- No systemic disease in the past
- Tattoo of eyebrow since age of 23
- Known to have hepatitis C for 7 years
- Received interferon therapy for acute hepatitis C 5 years ago
- No blood transfusion
Physical Exam

- Multiple non-blanchable palpable painful purpura over bilateral lower legs and upper thighs
- Bilateral Gr. II pitting edema over bilateral lower legs
- Active synovitis over right ankle
- No lymphadenopathy, no sinus knocking pain, no wheezing, no focal weakness
What is your impression?
Differential Diagnosis

• (A) Senile purpura
• (B) Vasculitis
• (C) Immune thrombocytopenic purpura
• (D) Thrombotic thrombocytopenic purpura
• (E) Hepatitis C with liver cirrhosis and thrombocytopenia
Which ordinary tests would you like to order?
Lab Tests

- WBC: 4600, HgB: 8.3, PLT: 114K
- Cr: 1.8 mg/dl, BUN: 32 mg/dl
- AST/ALT: 69/70 U/l, Total Bilirubin: 0.4 mg/dl, Albumin: 4.1 g/dl, PT INR: 1.0
- HBsAg (-), anti-HBs Ab (+), anti-HCV (+)
- Urine routine: RBC 3+, WBC: 5-10, protein: 2+ 24hrs urine protein: 1.00 g
Wrist X Ray
Abdominal Sonography
Which immunologic tests would you like to order?
Immunology Profile

- ANA 1:80, fine speckled
- RF IgM: 55.2 IU/ml (Normal < 15 IU/ml)
- C3: 92.7 mg/dl (Normal 90~180 mg/dl)
  C4: 2.05 mg/dl (Normal 10~40 mg/dl)
- APS profile: all negative; ANCA: negative
- Cryoglobulin: 3.5% (Normal < 0.10%)
- CG typing: TYPE II: IgM KAPPA AND IgG KAPPA
- HCV RNA Quantification: 3200 copies/ml
Skin Biopsy

H & E Stain

leukocytoclastic vasculitis
What is your differential diagnosis?
Differential Diagnosis

• (A) Rheumatoid arthritis with vasculitis
• (B) Idiopathic hypersensitivity vasculitis
• (C) Essential mixed cryoglobulinemia
• (D) Henoch-Schönlein purpura
• (E) Schamberg disease
Final Diagnosis

- Hepatitis C infection with essential mixed cryoglobulinemia (type II) and renal involvement
## Classification of Vasculitis

<table>
<thead>
<tr>
<th>Arteriole/capillary venule</th>
<th>Small artery</th>
<th>Medium artery</th>
<th>Large artery</th>
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<tbody>
<tr>
<td>Takayasu’s arteritis</td>
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<td>Giant cell arteritis</td>
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<td>Classic polyarteritis nodosa</td>
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<td>Kawasaki disease</td>
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<td>Wegener’s granulomatosis</td>
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<td>Microscopic polyangiitis</td>
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<td>Churg–Strauss syndrome</td>
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<tr>
<td>Cryoglobulinemia</td>
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<td>Cutaneous leukocytoclastic vasculitis</td>
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<tr>
<td>Henoch–Schönlein purpura</td>
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### Typical Manifestations of Vasculitis

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<tr>
<th>Large</th>
<th>Medium</th>
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<tbody>
<tr>
<td>Limb claudication</td>
<td>Cutaneous nodules</td>
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<tr>
<td>Asymmetric blood pressures</td>
<td>Ulcers</td>
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<tr>
<td>Absence of pulses</td>
<td>Livedo reticularis</td>
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<tr>
<td>Bruits</td>
<td>Digital gangrene</td>
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<tr>
<td>Aortic dilation</td>
<td>Mononeuritis multiplex</td>
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<tr>
<td>Renovascular hypertension</td>
<td>Microaneurysms</td>
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<tr>
<td></td>
<td>Renovascular hypertension</td>
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<td>Purpura</td>
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<td>Vesiculobulloss lesions</td>
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<tr>
<td>Urticaria</td>
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<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Alveolar hemorrhage</td>
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<tr>
<td>Cutaneous extravascular necrotizing granulomas</td>
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<tr>
<td>Splinter hemorrhages</td>
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<tr>
<td>Uveitis/episcleritis/scleritis</td>
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Consideration in Vasculitis

Size of predominant blood vessels affected

Epidemiologic features
  - Age
  - Gender
  - Ethnic background

Pattern of organ involvement

Pathologic features
  - Granulomatous inflammation
  - Immune complex deposition versus pauci-immune histopathology
  - Linear staining along glomerular basement membrane

Presence of ANCA, anti-GBM antibodies, or rheumatoid factor in serum

Demonstration of a specific associated infection (hepatitis B or hepatitis C)

Secondary Vasculitis Syndromes

- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with other primary diseases
  - Infection
  - Malignancy
  - Rheumatic disease
Extrahepatic Manifestations of HCV

- Hematologic disorders: cryoglobulinemia and lymphoma
- Autoimmune disorders: autoimmune hepatitis, thyroiditis, sialadenitis, myasthenia gravis
- Dermatologic disease: porphyria cutanea tarda, leukocytoclastic vasculitis, lichen planus
- Diabetes mellitus, membranoproliferative glomerulonephritis, rheumatoid-like arthritis
Cryoglobulinemia

• Cryoglobulins are single or mixed immunoglobulins that undergo reversible precipitation at low temperatures.

Brouet classification

• Type I: a monoclonal immunoglobulin, usually IgM or IgG, IgA, or light chain. Ex. Waldenström's macroglobulinemia or multiple myeloma
Cryoglobulinemia (CG)

**Brouet classification**

- Type II: A mixture of polyclonal Ig in association with a monoclonal Ig, typically IgM or IgA, with rheumatoid factor activity, often due to persistent viral infections, particularly HCV and HIV infections.
- Type III: polyclonal Ig, often secondary to connective tissue diseases.

Types II and III represent 80% of all cryoglobulins.
Typical Presentation of CG (1)

- Cutaneous: erythematous macules, purpuric papules, ulcerations particularly in the lower extremities, Raynaud phenomenon, livedo reticularis

![Cutaneous small-vessel vasculitis](image1)

![Purpura in the trunk](image2)

- cutaneous small-vessel vasculitis
- purpura in the trunk
Typical Presentation of CG (2)

- Musculoskeletal: Arthralgias in >70% patients
- Renal disease: isolated proteinuria and hematuria, secondary to thrombosis (type I) or immune complex deposition (types II and III),

membranoproliferative glomerulonephritis
Typical Presentation of CG (3)

- Neuropathy: affecting around 70% CG patients, peripheral neuropathy, mononeuropathy multiplex.
- Arterial thrombosis, Sicca symptoms, abdominal pain, interstitial lung disease, hepatosplenomegaly, lymphadenopathy.

**mononeuritis multiplex**

**acrocyanosis**
Treatment

- Treat underlying diseases (IFN-$\alpha$ + ribavirin)
- Glucocorticoid, cyclophosphamide, azathioprine
- Plasmapheresis for life-threatening complication
- Rituximab

Take Home Messages

• Palpable purpura is suggestive of systemic vasculitis. Systemic review is warranted.
• Hepatitis C infection is associated with hepatic and extra-hepatic manifestations.
• Check cryoglobulin, RF, C4, CG typing once cryoglobulinemia is suspected.
• Treat underlying disease (malignancy, chronic virus infection or autoimmune disease) is the first priority.