Renal vascular diseases
CPC
G.A. Appel MD
M.B. Stokes MD

Case 1

- A 36 year old previously healthy female develops fever and bruising. She goes to her LMD and CBC shows plats 15 K, Hct 28%, normal PT and PTT.
Case 1

- Smear shows microangiopathic hemolytic anemia.

- Over next few days her urine output declines and she develops sudden blindness followed by decreased mental status.

- A renal biopsy is performed.
Glomerulus with thrombus

Platelets and RBCs
Arteriole with thrombus

Entrapped RBCs in arteriole wall
Case 1

- Pathologic findings: Thrombotic microangiopathy
- Diagnosis: Thrombotic Thrombocytopenic Purpura (TTP)

Followup:
- She is treated with plasma exchange.
- An assay for metalloprotease shows marked reduction (ADAMTS 13).
- Over the ensuing weeks her mental status improves, vision returns, and renal function improves.
Thrombotic thrombocytopenic purpura (TTP)

- Familial or acquired
- Single episode, or relapsing
- F:M 3:2
- Peak in 3rd decade
- CNS, other extrarenal signs often predominate (e.g. fever; purpura; heart failure; lung edema; elevated LDH)
- Acute renal failure; microangiopathic hemolytic anemia; thrombocytopenia

ADAMTS 13

A disintegrin and metalloprotease, with TSP-1-like domains (aka vWF-clearing protease)

Protease, normally degrades vWF multimers

Deficiency → platelets GPIbα ↔ vWF multimers

Mutations or autoAb
ADAMTS and TTP

Criteria for Inclusion of TTP Cases

Presence of thrombocytopenia & microangiopathic hemolysis
No plausible causes
No features suggestive of typical or atypical HUS
Age > 10 yr

127 Cases in 4 yrs – All severe ADAMTS 13 deficient

Case 2

- A 4 yo female child goes to a petting zoo with her parents. She cuddles the sheep, calves, and other baby animals. She does not wash her hands immediately afterwards.
- 3 d later she develops abdominal cramps, diarrhea, and bloody stools. N/V, fever. Given antibiotics by pediatrician.
- Day 6 echymoses of extremities and lips, thrombocytopenia, oliguria, and seizures.
- Stool is + for E.coli O157:H7.

Case 4: E.coli-associated HUS

Pathologic findings
Colon: hemorrhagic necrosis

Fibrin/RBC thrombi
Thrombus (trichrome stain)

Cortical necrosis
Case 2

- Diagnosis: Shiga toxin-related (Stx+) hemolytic uremic syndrome (D+HUS)
Consumers warned not to eat fresh spinach imported from U.S.

BY MARTIN MITTELSTAEDT

Canadians shouldn't eat any fresh spinach imported from the United States until further notice, a precautionary move to avoid confirming E. coli contamination, says the Canadian Food Inspection Agency.

The agency issued the call yesterday afternoon, prompting grocery chains across the country to pull all U.S.-grown spinach and any prepared salads containing the vegetable from U.S. sources from store shelves.

Companies supplying the restaurant trade with fresh salad ingredients have also stopped shipments.

The action was taken even though there have been no confirmed cases of E. coli poisoning in Canada from eating fresh spinach.

This is public in the United States, where a deadly E. coli outbreak believed to be associated with eating fresh spinach has caused one death and sickened at least 64 people.

Produce wholesaler Joseph Mercurio looks over bags of spinach packed at a facility in the United States.

Said Cardinal, a CFIA spokesperson, who called the step a precaution. "Currently, there are no illnesses reported in Canada that are directly linked to this outbreak in the U.S."

At this time of year, Canadian-grown spinach is also on the market and it is not affected by the advisory. Bags are supposed to carry a country of origin allowing consumers to identify their source.

The effort to pull spinach from store shelves began about 3:30 yesterday afternoon, when major grocery chains started removing the product, according to Tim Sherwood, a spokesperson for the Canadian Council of Grocery Distributors, a trade group that represents most of the country's major supermarket chains, as well as companies that serve the restaurant trade.

"Everyone feels it's better to be prudent," Mr. Sherwood said.

"Eating food contaminated with..."
Childhood HUS

- **STx Associated**
- **2.1 per 100,000 /yr** peak < 5 yo
- **Warm summer months**
- **Onset GI sx, cramps, diarrhea, n/v, fever**
- **70% bloody diarrhea w/i 2 days**
- **E.coli 0157 3-7% sporadic, 20% epidemic**
- **STx – E coli in stool for wks**
Role of Shiga Toxin

- Epidemics with hemorrhagic colitis +/- HUS
- Epidemics in fast food outlets
  - E. coli 0157:H7
- Sporadic HUS same
- A filterable agent in stool causes Hem. Colitis & cytopathic to green monkey kidney cells (verotoxin)
- E. Coli 0157:H7 produce both STX1 and STX2

Transmission of E. Coli - STX

- E. coli in cattle (& other animals) – manure, water troughs, farms
- Transmit by food or water
- Usually beef contaminated at slaughter
- Also raw milk, fruit & veg, apple cider, apple juice
- Person to person – day care centers
Shigatoxin-1 and Endothelium

- Binds to Gb3 on glomerular endothelium
- Gb3 expression equal in children vs. adults
- Mechanism for childhood susceptibility remains undetermined

Ergonul, Clayton, Fogo, Kohan, 2003

Verotoxin

- A subunit binds 60S Ribosomes, inhibit protein synthesis
- 5 B subunits binds glycolipid receptors (gb3) on surface of colonic epithelium, endothelium, and WBCs
Shiga Toxin and Cell Injury

Moake, NEJM 2002

Higher Risk HUS

- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females
Course ARF Childhood HUS

- 50% dialysis
- 75% transfusions
- 25% Neuro sx (CVA, sz, coma)
- 3-5% die in acute phase
- Long term renal dysfunction common

Residual Renal Disease in Childhood HUS

- 3-18% ESRD
- 10-40% low GFR, proteinuria, CRF, HBP
- Duration anuria predicts dysfunction
  - 7.5% anuria < 10 days low GFR
  - 42.5% anuria > 16 days low GFR
Case 3

- An 28 year old male has a hx of TTP-HUS at age 12 yo. He progressed to ESRD slowly over a few years, and has a Hx of a renal txp from his mother at 20 yo elsewhere that failed 3 months post Txp. His brother is a dialysis patient as well.
- The bx report from the failed Txp reads “thrombotic microangiopathy”.
- The patients complement values are low especially his C3 level.
- His father is offering him a kidney. Should he take it?

Case 3

- Diagnosis: Atypical Hemolytic Uremic Syndrome (D–HUS)
Atypical Hemolytic Uremic Syndrome

- Atypical hemolytic uremic syndrome = Shiga Toxin Negative HUS.

- Most cases due to continuous activation of the alternate complement system due to genetic defects in regulatory proteins Factor H, Factor I or MCP.

- Some cases due to antibodies that alter the action of these complement regulatory proteins.

- In some patients liver transplant along with kidney transplant is the therapy of choice (to replace the missing complement inhibitor)

- Registry of non-STx HUS/TTP includes 164 centers worldwide; Total pts = 412 (familial 85, sporadic 327)
Thrombotic thrombocytopenic purpura (TTP)

- CNS signs predominate
- Deficiencies of vWF cleaving metalloproteinase (ADAMTS13), either
  - Hereditary (rare)
  - Acquired (autoantibodies)

Thrombotic microangiopathy: diverse etiologies

- Tumor emboli
- HUS (Shiga toxin)
- Other causes
- Atypical HUS
- DIC
- Vasculitis
- Bone marrow transplant
- Allograft rejection
- Drugs

Dysfunction of organs
Thrombocytopenia
Fragmentation of red blood cells

Wolf G. NDT 2004
Case 4

- 27 yo F stock analyst has a hx of three spontaneous abortions, and Raynaud’s phenomenon. Two years ago she developed a DVT of the right calf after a long auto trip. She develops arthralgias, low temps, and malaise.

- Px BP 152/92, P 84, malar flush, 2/6 SEM, swollen MCP and PIP joints, livedo reticularis of legs and arms, 2+ ankle edema.

  WBC 3.6 K, Hct 24%, plts 89K
  U/A 4+ prot, 3+ heme, 8-15 rbc, + rbc casts
  BUN 43 mg/dl, Pcreat 2.6 mg/dl, 24 hr UV prot 1.8g/d, PT 14.6, PTT 85.
  ANA + 1:160, anti-dsDNA negative, complement borderline, + VDRL.

Case 4

Diagnosis: Antiphospholipid antibody Syndrome (anticardiolipin syndrome)
Antiphospholipid Antibodies

- Family of Antibodies (IgG, IgM, IgA) against negatively charged phospholipids
- Lupus Anticoagulant - Abs that prolong lipid dependent coag tests, interfere with phospholipid of the prothrombin activator complex.
- Anticardiolipin antibodies - Abs that bind to cardiolipin (phospholipid antigen used in tests for syphilis)
- False + VDRL
- Procoagulant Effect in vivo

Underlying Conditions with Antiphospholipid Antibodies

- Systemic Lupus Erythematosus
- "Lupus-Like" Syndrome
- Primary Anti-phospholipid Syndrome
Clinical Manifestations Related to Anticardiolipin Antibodies

- Recurrent arterial and venous thromboses
- Placental thromboses and spontaneous abortions
- Livedo reticularis
- CNS complications
- Pulmonary Hypertension

Extrarenal Manifestations of APLS (65%)

- CNS disease 8
- Deep vein thrombosis 6
- Myocardial infarction 4
- Pulmonary embolism 4
- Livedo reticularis 4
- Adrenal disease 3
- Other (aortic thrombosis with RAS, bowel infarction, miscarriage) 3

Total 17/26
Serologies and Lab Data

- Prolonged PTT 12/26 (46%)
- Thrombocytopenia 9/23 (38%)
- +ANA 15/26 (58%)
- +AntiDNA 2/24 (8.3%)
- Low complement 7/24 (29%)
- False positive VDRL 6/11 (55%)

Clinical Presentation at Biopsy

- Hypertension 16/26 (62%)
- Active urine sediment 10/26 (38%)
- Serum creatinine (mg/dl) 2.0 +/- 0.22
- Proteinuria (g/day) 4.4 +/- 0.87
- Nephrotic Syndrome 15/26 (58%)
Case 4: Antiphospholipid antibody syndrome

Pathologic findings
Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman’s space)

Glomeruli show segmental intracapillary fibrin
Arteries show widespread luminal narrowing with extensive subendothelial hyalinosis, endothelial swelling, focal myocyte dropout, focal mucoid intimal fibroplasia, and focal intramural fibrin with entrapped red blood cells.

Artery shows intimal expansion and luminal obliteration.
Artery shows fibrin thrombus and entrapped RBCs

Artery with fibrin thrombus
Recanalized artery (healed thrombus)

Fibrin
Case 5

- 70WM with longstanding HTN
- Mild CKD
- BP becomes increasing difficult to control
- Renal MR angiogram performed
Renal artery stenosis

Renal artery atherosclerosis
Case 5 (cont’d)

- Rx: Angioplasty
- BP stabilizes but then develops ARF, rash, eosinophilia
- Renal biopsy performed
Case 5

- Renal biopsy findings:

Hypertensive nephrosclerosis

Finely granular surface
Hypertensive nephrosclerosis

Thin renal cortex

Hypertensive arteriolosclerosis

Arteriolar sclerosis and hyalinosis
Case 5

Diagnoses:
- 1. Renal atheroembolic disease
- 2. Hypertensive arterionephrosclerosis