Case Report: HLH triggered by Lupus Nephritis

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Case

- 6 year East Asian female presenting with:
  - Fevers x 3 weeks, no pattern, Tmax 104.7
  - Periumbilical pain x 1 week
  - Decreased PO x 4 days
  - Dysuria x 1 day
- Non-contributory medical history (Birth/PMH/PSH/Social)
  - Born FT via repeat C/S
- No chronic conditions, no medications
- UTD on all age-appropriate immunizations
  - COVID vaccinated

Pertinent History

- Several family members previously sick with self-limited URI's
- Seen previously by PCP 1 week prior
  - Rapid COVID, Influenza, and Strep tests all negative
  - Conservative management
- ROS also (+) for: facial flushing with fevers, questionable upper/lower extremity edema
- ROS pertinent (-)'s: Conjunctivitis, mucositis, cervical LAD, polymorphous rash, hematuria, petechiae

ED Course (4/14)

- VS: T 103.1, remainder WNL
- Labs:
  - **Pancytopenia** (WBC 2.7, Hb 9.1, Plt 105), UA: **300 protein**, 1+ bacteria, 5-10 WBC, neg LE and nitrite, **large blood**. K 5.2, **Cr 1.81** (no b/l), BUN/Cr 38, AP 172.
  - **ESR 45**, **CRP 0.30**, **LDH 669**, **Ferritin 2500**
  - **BNP 2124**, trop 29
  - RVP w/ COVID PCR: **negative**, COVID Ab: **(+)/Reactive**
  - BCx/Ucx ordered
- Imaging:
  - Abd U/S, Limited: no findings
  - CXR: No acute process
  - Complete Abd U/S: No hydronephrosis, nonspecific debris in bladder
  - **Echo: Normal anatomy, flow, function. No aneurysms.**
- EKG: Normal
- Treatment: 800 cc NS, CTX 1g x1, Tylenol and Motrin x1, started on MIVF D5 LR

Examination

- General no distress, well developed, well nourished, non-toxic appearing, no evidence of wasting
- HEENT no dentition abnormalities, normocephalic/ atraumatic and oropharynx clear, **dry mucous membranes, lips without obvious cracks/fissuring, no lingual abnormalities noted**. No appreciable cervical LAD > 1.5 cm.
- Eyes Conjunctivae Clear Bilaterally, no appreciable injection
- Neck full range of motion and supple
- Respiratory Clear Breath Sounds Bilaterally, No Increased Effort and Good Air Movement Bilaterally
- Cardiovascular RRR, S1S2, No murmur, No rub, No gallop and Radial/Pedal Pulses 2+/=
- Abdomen soft, **mild to moderate TTP to periumbilical region without guarding or rebound**, non distended, **mild splenomegaly**, no appreciable hepatomegaly, active bowel sounds and no masses
- Skin **Mildly flush/erythematous cheeks more prominent with fever, no petechiae**
- **Musculoskeletal mild pitting edema to distal BLE's**
- Neurology CN II - XII grossly intact and sensation intact

Differential

- Nephro:
  - **Nephritic syndromes**: PSGN, IgA nephropathy, Alport syndrome, Lupus
  - **Nephrotic syndromes**: Minimal change disease, membranous nephropathy
- Cardiac/Immunologic: **MIS-C**, **Atypical/Incomplete Kawasaki**
- ID: **HUS**, CMV, EBV, Parvovirus, Histoplasma capsulatum
- Rheumatologic: **SLE**
- Heme/Onc: Hemophagocytic lymphohistiocytosis (**HLH)**, Hereditary spherocytosis, **TTP**, aplastic anemia, myelofibrosis, myelodysplastic syndrome, **leukemias**

Hospital Course

- Day 1 (4/15)
  - Labs:
    - Heme:
      - Coag studies: Fibrinogen and PT/INR WNL. **PTT 45.6** (H). **D-dimer 20.32**.
      - **Haptoglobin <8** (L)
      - **Reticulocyte Index: 0.3** (Hypoproliferative)
      - Peripheral smear ordered
    - Lipid panel: **TG 411**, LDL 60
    - Nephro:
      - Urine protein/Cr: **2.7** (Nephritic favored)
      - Uric acid: 7.5 (H)
    - Rheum/Immuno: **ANA (+)** w/ reflex panel pending, **C3>20** (L), **C4>5** (L). Anti dsDNA IgG and Anti-Sm Antibodies ordered
    - ID: EBV, Parvo, CMV PCR's, Shiga toxin
  - Imaging:
    - Repeat Abd U/S (Complete): **Borderline splenomegaly**, trace ascites, remainder normal
  - Cardiology Consulted: Agreed with holding off on IVIg, low index of suspicion for MIS-C or Atypical Kawasaki

Hospital Course

- Fevers persisted; alleviated with alternating Tylenol and Ibuprofen
- Case discussed with VCU Heme/Onc: Check IL-2 receptor for HLH, recommended bone marrow biopsy, bed available
- Case discussed with VCU Nephrology: Recommended renal biopsy
- Discussion with family regarding transfer – opted to stay a night

Hospital Course

- Day 2 (4/16)
  - Pancytopenia worsened (Platelets 105 > 69)
    - ANC < 0.5
    - IV Cefepime started
  - Critical call from pathology: (+) schistocytes > advised transfer, c/f TTP
  - Discussed with family and VCU Heme/Onc, patient accepted and transferred

Course at VCU (4/16-4/23)

- Working diagnosis was HLH triggered by SLE or viral illness (CMV/EBV/Parvo)
- Received 1u pRBC and 1u Platelets prior to BM Biopsy and LP
- Prelim BM Bx results c/f HLH: started on high dose steroids
- LP CSF Cell count: No findings
- Labs ordered:
  - Genetic testing for HLH
  - CXCL9
- Original Echo read again by VCU-Cards; concerning for coronary artery dilatation. Incomplete KD vs complication of HLH. Held on IVIg.

- HLH 5/9 for diagnosis:
  - **Fever ≥38.5°C/101.3F**
  - **Splenomegaly (Questionable)**
  - **Peripheral blood cytopenia**, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL
  - **Hypertriglyceridemia** (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
  - Hemophagocytosis in bone marrow, spleen, lymph node, or liver
  - Low or absent NK cell activity
  - **Ferritin >500 ng/mL** (the authors prefer to consider a ferritin >3000 ng/mL as more indicative of HLH [83])
  - Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms
  - Elevated CXCL9 [176]

Course at VCU (4/16-4/23)

- Labs from St. Mary's resulted:
  - Anti dsDNA Ab: 30 (H)
  - Antichromatin Ab: 5.9 (H)
  - SS-A, SS-B, Smith, RNP, Jo-1, Centromere Ab's all negative
  - ID: CMV, Parvo, EBV PCR's negative, Shiga Toxin negative
- Received 1u pRBC and 2u platelets pre- and post-op **Renal biopsy** on 4/20
  - **Prelim findings c/w lupus glomerulonephritis**
- Soluble IL-2 elevated, but below threshold for HLH
- Given IVIg x1 to initiate treatment of lupus nephritis > First Cyclophosphamide infusion

Course at VCU (4/16-4/23)

- High dose steroids stopped > transitioned to PO pred taper
- Clinical improvement noted following IVIg and first infusion of Cyclophosphamide.
  - Thrombocytopenia and leukopenia resolved
  - Remained mildly anemic, but improved
- Genetic testing: non-contributory
- Final Renal Bx: Class IV (Diffuse) Lupus Nephritis
- Final BM Bx: HLH, immunostains non-contributory, no evidence of NHL or acute leukemia.
- Close follow-up advised with Nephro
  - Cyclophosphamide infusions, once a month for 5 more doses

Brief Summary

- HLH:
  - Risk factors: Certain genetic markers
  - Yearly incidence: Per large multi-hospital/country study = **1.5 per million ped admissions.**
  - Pathogenesis: Pathologic hyperactivity of CD8+ T cells and macrophages. Hemophagocytosis > pancytopenia. Cytokine storm.
  - Etiology: Often genetic in peds, but triggered by viral infections, malignancy, or **rheum disorders**.
  - Presentation: Fevers, **pancytopenia**, **hepatosplenomegaly**.
  - Diagnosis: 5/9 criteria as discussed previously. **Elevated ferritin**, D-dimer, CRP, procal good markers to guide work-up.
  - Treatment: Underlying cause. High dose steroids. Immunosuppressives.
- Lupus Nephritis:
  - Epidemiology: occurs in about 50% pt's with SLE. Some genetic links.
  - Pathogenesis: Deposition of anti-dsDNA immune complexes in glomeruli > inflammatory response > renal damage + low C3 and C4 levels.
  - Presentation: **Proteinuria**, hematuria, elevated Cr, +/- RBC Casts. **Low C3 AND C4 are good markers**.
  - Diagnosis: Definitive = Biopsy.
  - Treatment:
    - Initial: Steroids + either Cyclophosphamide or mycophenolate mofetil (MMF). Some evidence for IVIg, case specific.
    - Subsequent: May continue Cyclophosphamide OR MMF if adequate response achieved. Alternative is Azathioprine.

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