Objective:
- Describe features of the COVID19 multisystem inflammatory syndrome in children
- Recognize dermatological manifestations of proteosome associated autoinflammatory disease

Case:
10-year-old healthy girl
CC: Sore throat, abdominal pain, subjective fever x 3 days
On Day 3 of Amoxicillin for presumed strep throat
PMH: Henoch Schonlein Purpura (2 years prior)
ALL: NKDA
Fever 102 F, tachycardic, ill-appearing

Question: Is this erythema multiforme?
DDx

- Urticaria Multiforme
- Erythema multiforme

Serum sickness like reaction

Mucous membrane erosions?
“eyes are red and lips slightly peeling”

- 10 years old
- Fever to 102 F x 3 days
- Tachypnea
- Tachycardia
- Severe abdominal pain
- No lymphadenopathy

Kawasaki Disease (KD)

Polymorphous exanthem
- macular
- papular
- morbilliform
- urticarial
- scarlatiniform

- KD eruption generally starts on trunk
- In one large series, KD started in diaper area in 62%
- Petechial rash and desquamation may be a supportive clue if other findings present

- 80% cases in children < 5 years old
- 50% cases in children < 2 years old
- Winter-spring seasonality
Classical Kawasaki disease in COVID19 positive child


### Classical Kawasaki Disease

- **Morphology**
  - Polycyclic wheals +/- ecchymotic centers
  - Classic small target lesions
  - Often acral

- **Fixed lesions**
  - No

- **Facial/acral edema**
  - Common

- **Dermatographism**
  - Yes

- **Mucous membranes**
  - No

- **Duration**
  - 2-12 days

- **Characteristic features**
  - Low-grade fever
  - Viral infection symptoms
  - High-grade fever
  - Sick appearing
  - Arthritis
  - Lymphadenopathy
  - Acute infection

- **Adapted from Shah, K et al. Pediatrics 2007**

### Labs

- SARS Co-V2 NP PCR: negative
- SARS Co-V2: IgM positive
- SARS Co-V2: IgG negative

- WBC 16-4k
- Absolute lymphocytes low
- CRP 14
- ESR 80
- Elevated: D-dimer, ferritin, LDH
- UA 2+ blood
- Elevated BNP
- Elevated troponin
- Echocardiogram: Decreased LV systolic function

### MISC: Multisystem Inflammatory Syndrome in Children

- **CDC definition:**
  - < 21 years of age
  - Fever ≥ 24 hours
  - Elevated CRP, ESR, fibrinogen, D-dimer, ferritin, LDH, IL6, neutrophilia, lymphopenia, and low albumin
  - Clinically severe illness requiring hospitalization
  - ≥ 2 organs involved (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), AND
  - No alternative plausible diagnosis, AND
  - Positive for current or recent SARS-CoV2 infection by RT-PCR, serology (IgG/IgM), or antigen test; or COVID-19 exposure within 4 weeks prior to the onset of symptoms

### MIS-C spike after COVID19 surge in NYC 2020

- MIS-C lags 2-4 weeks after COVID19 infection

- Figure: Pediatric Cases of Coronavirus Disease 2019 (COVID-19) or SARS-CoV2 infection and MIS-C


MIS-C


Mucocutaneous Findings in MIS-C

- Retrospective case study of 35 children
- 25 met MIS-C criteria, 10 probable MIS-C
- 29/35 (83%) exhibited mucocutaneous changes
  - Conjunctival injection (n = 21)
  - Erythematous plaques (n = 18)
  - Lip erythema (n = 17)
  - Periorbital edema and ecchymosis (n = 7)
  - Strawberry tongue (n = 8)
  - Malar erythema (n = 6)

- Mucocutaneous findings occurred a mean of 2.7 days (range, 1.7 days) after the onset of fever
- Mucocutaneous findings were not associated with poorer outcomes

Young TK et al. JAMA Dermatol. 2021 Feb 1;157(2):207-212

Retrospective study of mucocutaneous symptoms in children admitted for COVID19 or MIS-C

Young TK et al. JAMA Dermatol. 2021 Feb 1;157(2):207-212

Summary: MIS-C

Multisystem inflammatory syndrome in children
- Triggered by COVID19 infection
- Up to 4 weeks after COVID19 infection
- Fever (>38°C)
- Multi-organ involvement

Mucocutaneous findings: “Kawasaki-like phenotype”
- Bilateral non-exudative conjunctival injection
- Peri-orbital edema
- Dry, cracked vermilion lips
- “Kawasaki-like dermatitis”, palmar erythema
- Erythematous macules/papules, maculopapular, macular, lacunar, urticarial, vesicular
- Palmar and plantar erythema


Autoinflammatory Disease vs. Autoimmune Disease

- Malfunction of innate immune system
- Neutrophil mediated
- “Host vs. danger signal”

- Malfunction of adaptive immune system
- Lymphocyte mediated
- “Self vs. non-self”

Fevers
“Rash”
Joint pain and swelling
Fatigue
5 Signs of Autoinflammatory Disease in Children

1) More than 3 episodes of fever >101 F with no explained infectious etiology
2) Predictable course of each episode
3) Specific symptoms during episodes
   · Skin eruptions (non-pruritic)
   · Joint or bone pain
   · Severe abdominal pain
   · Conjunctivitis with no upper respiratory infection symptoms
4) Episodes are triggered by specific stimuli
   · Cold exposure
   · Vaccines
5) Family history of autoinflammatory disease or amyloidosis

Two or more of these 5 signs may suggest autoinflammatory disease


Systemic Autoinflammatory Disorders (SAID)

- MEFV Familial Mediterranean Fever
- More than 30 genes identified for SAID disorders
- At least 40-60% of patients with a SAID phenotype do not have a defined diagnosis

Average time from disease onset to diagnosis of a SAID = 7.3 years


Case

Symptoms
- Recurrent fevers > 102 F
- Migraines
- Transient migratory arthritis
- Elevated CRP, ESR
- Hospital admission for septic meningitis

Family History
- No family history of autoimmune disease or immunodeficiency

Medications
- Methotrexate 0.8 mg/kg PO weekly
- Prednisone 0.5-1 mg/kg PO daily
- IVIG q 4 weeks

http://www.nomidalliance.org/
GENETIC SEQUENCING

Compound heterozygous mutation in the PSMB8 gene

CLINICOPATHOLOGICAL CORRELATION

- Recurrent annular erythematous plaques
- Pecers, myalgias, arthritis, aseptic meningitis, elevated acute phase reactants
- Dense, atypical, mixed mononuclear and neutrophilic dermal infiltrate
  - Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

CANDLE

- Autosomal recessive inheritance
- Homozygous or compound heterozygous mutation in the PSMB8 gene (proteasome subunit beta-type 8)
  - PSMB8: proteosome subunit involved in proteolysis and maintenance of cell homeostasis
  - Proteosomes degrade proteins produced by dead or stressed cells
- In CANDLE syndrome, dysregulation with increased Type 1 Interferon signaling

CANDLE: Treatment

- High dose corticosteroids (1-2 mg/kg/day)
  - Improves cutaneous eruption, joint pain, and fever
  - Disease flares with tapering
- Steroid-sparing agents (methotrexate, cyclosporine, azathioprine, IVIG)
  - Poor response in some patients
- TNF-α inhibitors
- IL-1 receptor antagonists
- JAK inhibitors
- NIH clinical compassionate use research trial (baricitinib, JAK1/2 inhibitor)
Case:

- Recurring erythematous nodules
  - 2 additional skin biopsies with dense neutrophilic infiltrates consistent with Sweet syndrome
  - Neutrophilic dermatosis did not improve with prednisone
- Frequent infections
  - Rhinovirus pneumonia
  - Mycobacterial pneumonia
  - Prolonged astrovirus enteritis
  - Prolonged salmonella enteritis
  - Salmonella bacteremia
- Positive autoantibodies
  - FANA, anti-thyroid antibody
  - Type I interferon cytokine profile

PRAID: treatment

- PRAID is a Proteasome Associated Autoinflammatory Syndrome (PRAAS)—but with profound immunodeficiency
- Concern for JAK inhibitor use as already experiencing severe and opportunistic infections
- Hematopoietic stem cell transplant in 2 PRAID patients was curative
- Pomp is ubiquitously expressed
- The clinical and immunological features of PRAID are predominantly derived from a proteasome defect in hematopoietic cells

Sweet syndrome in neonates

- Uncommon
- In the first 6 weeks of life, frequently associated with underlying disease
  - Most often associated with
    - Primary immune deficiency
    - Autoimmune disorders
    - CANDLE
    - PRAID
  - Less commonly associated with
    - Malignancy
    - Secondary immune deficiency (HSV)
    - Neonatal lupus
- May result in scarring, sometimes atrophic

- 2-week-old boy admitted to NICU with fever and concern for seizure
  - Thrombocytopenia
  - Hyperesinophilia
  - Rare blasts on peripheral smear

HSV/VZV lesional PCR negative
Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

PRAID: POMP Related Autoinflammation and Immune Dysregulation

Early onset neutrophilic dermatosis
Lipodystrophy
Recurrent infections
Arthralgia
Autoantibodies
Increased Type I interferon signaling
Recurrent fevers
Aseptic meningitis
Thrombocytopenia

THANK YOU