VASCULITIS

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Introduction

What is Vasculitis?

- An inflammatory destructive process affecting arteries and veins. It might include infiltration of the vessel wall by inflammatory cells without destruction.
- **Etiology:**
  - Primary: autoimmune
  - Secondary: due to another cause, like infection, malignancy, drug exposure, rheumatic condition.

Where could we find Vasculitis?

  - It could involve the skin, like cutaneous Vasculitis.
  - OR the internal organs, like isolated angiitis of the CNS which is an inflammation of the walls of small blood vessels that **affects only the vessels in the CNS.**
  - OR both skin and internal organs, like the systemic Vasculitis.
- Vasculitis is classified according to the size of involved vessels into:
  - large size vessel vasculitis
  - Medium size vessel vasculitis
  - Small size vessel vasculitis

What are the suggested mechanisms that explain Vasculitis?

There are three major mechanisms:

  - Immune complex chemoattractant hypothesis.
  - Adhesion molecules.
  - Antibody mediated vascular injury.

What are the conditions that may mimic systemic Vasculitis?

- Drug exposure: cocaine, amphetamine, penicillin, sulfa drugs, anticonvulsants, hydralazine, propylthiouracil.
- Infections
- Malignant disease
- Atrial myxoma
- Cholesterol emboli
- Antiphospholipid antibody syndrome
- Other connective tissue disorders

What are the infections that may cause Vasculitis?

- Viral: HIV, Hepatitis B,C, EBV, herpes zoster, Parvovirus B19 and CMV.
- Bacterial: Subacute Bacterial Endocarditis (SBE)
- Spirochetal: syphilis
- Rickettsial: Rocky Mountain spotted fever

Types of Vasculitis

1. **large size vessel Vasculitis:**
   - **Giant cell (temporal arteritis)**: affects the aorta and its major branches with a predilection for the extracranial branches of the carotid (often involves the temporal artery). May affect children but mostly occurs in patients older than 50 years.
   - **Takayasu arteritis (Pulseless disease)**: an inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
2. **Medium sized vessel Vasculitis:**
   - **Polyarteritis nodosa (PAN)**: necrotizing inflammation of medium sized or small arteries without glomerulonephritis or Vasculitis in arterioles, capillaries or venules.
   - **Kawasaki disease:** will be explained in details.
3. **Small vessel Vasculitis:**
   - **Granulomatous**
     - Wegner's granulomatous
     - Churg-Strauss syndrome
   - **Non-granulomatous**
   - Microscopic polyangitis
   - Henoch-Schonlein pupura (will be explained in details)
   - Cutaneous leukocytoclastic angitis

Henoch-Schonlein Purpura (HSP)

- IgA mediated small vessel vasculitis of an unknown etiology.
- Characterized by inflammation of small blood vessels with leukocyte infiltration of tissues, hemorrhage and ischemia.
- **The most common** systemic vasculitis in children.

Epidemiology

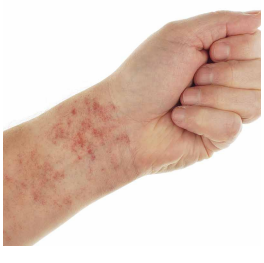
- 90% of the cases are reported in children.
- 50% of childhood cases are often preceded by URTI and/or strep pharyngitis.
- Occurs primarily in children (3-15) years, peak incidence (4-6)
- Slightly more common in boys than girls, M:F = 1.5:1
- Occurs more frequently in winter than summer months.

Etiology

- Although the mechanism is not that well known but the most likely mechanism is thought to be immune complexes mediated disease with deposition of IgA in glomerular capillaries, dermal capillaries and GI tract capillaries.
- The immune complexes associated with HSP are predominantly composed of IgA.
- Some drugs also may precipitate angiitis, like Vancomycin, streptokinase, Ranitidine.
- Food hypersensitivity, cold exposure, myelodysplastic syndrome, small cell lung disease, and breast cancer can also lead to HSP.

Characteristics of HSP

- **Palpable purpura rash** that begins as macules and rapidly progresses to purpura and ecchymosis.
- The rash can also be accompanied with **edema** and **joint swelling**.
- Palpable purpura are **non-blanching** and this differentiates it from ITP in which the rash can't be felt and it is blanchable.
- The rash most commonly appears bellow the wrist, in the buttocks and lower extremities (gravity areas).
- The whole mark of HSP is palpable purpura caused by small vessels inflammation in the skin leading to extravasation of blood into the surrounding tissue. So, there is no diagnosis of HSP without the **palpable purpura**.



- **Arthritis**: 80% in the lower extremities (ankle and knee most commonly involved), acute and painful, self-limiting.
- **GI involvement**: (50% of affected children)
    - Most typically: mild to moderate **cramping abdominal pain** (small vessels involvement leading to ischemia).
    - Less commonly: abdominal distention, constipation, bloody diarrhea, intusseption, abdominal perforation.
    - Seen during the acute phase, may precede the onset of rash.
    - Any child with recurrent history of HSP who presents with acute abdominal pain, obstipation or diarrhea should be evaluated for intussusception.
- **Glomerulonephritis**: (one third of patients)
    - Can be acute (hematuria, hypertension) or chronic.
    - It may present with hematuria or have mild glomerulonephritis leading to microscopic hematuria that can lead rapidly into progressive glomerulonephritis with RBC cast.

- The most common presentation of glomerulonephritis is the presence of RBC cast along with other manifestations like volume overload, hypertension and encephalopathy.
- Most common glomerulonephritis cases occur within the first month of presentation.
- The renal involvement usually resolves spontaneously if there is mild glomerulonephritis.

Investigations

- Elevated WBCs, CRP and ESR
- Platelet count is the most important test, because HSP is characterized by non-thrombocytopenic purpura with a normal or even high platelet count which differentiates it from other causes of purpura that are associated with thrombocytopenia such as autoimmune thrombocytopenia, SLE, leukemia.
- Urine analysis screening for evidence of hematuria.
- Serum blood urea nitrogen and creatinine should be obtained to evaluate renal function.
- Testing the stool for blood may identify evidence for gut ischemia.
- Any question for gut perforation requires radiologic investigations.
- Elevated IgA can be seen in 50% of cases.
- Post streptococcal glomerulonephritis has decreased levels of serum C3.

How to diagnose a patient with HSP?

According to Nilsson's test book: The diagnosis of HSP is based on the presence of two of the four listed criteria bellow:

***if there is no palpable purpura the diagnosis can't be made**.

1. Palpable purpura: Raised, palpable hemorrhagic skin lesions in the absence of thrombocytopenia.
2. Bowl angina: Diffuse abdominal pain or the diagnosis of bowl ischemia.
3. Diagnostic biopsy: Histologic changes showing granulocytes in the walls of arterioles or venules, IgA deposits in vessel wall.
4. Pediatric age group, less than 20:
    i. If a biopsy is taken from the skin the dermatological findings would be Leukocytoclastic vasculitis with IgA deposition.
    ii. And if it taken from the kidney, granular deposits of IgA, mesangio-proliferative glomerulonephritis, crescent formation will be found.

Treatment

- Therapy of HSP is supportive.
- A short-term course of NSAID can be administered for acute arthritis.
- Corticosteroids usually are reserved for patients with GI disease and provide significant relieve of abdominal pain.

- Acute nephritis typically is treated with corticosteroids but may require aggressive immunosuppressive therapy.

Complications of the Disease

- Most cases are monophasic, lasting 3 to 4 weeks and resolve completely.
- The rash can wax and wane for 1 year after HSP.
- The arthritis of HSP doesn't leave permanent joint damage.
- GI involvement can lead to temporary abnormal peristalsis that poses a risk of intussusception with bowl perforation.

Kawasaki Disease

- **Kawasaki disease**: Vasculitis of unknown etiology characterized by multi-systemic involvement. Mostly it affects **medium** sized arteries resulting in aneurism formation with a preferential involvement of the coronary arteries.

Epidemiology

- The second most common cause of vasculitis in childhood.
- High frequency in Japan.
- Male: female = 3:2
- The most common cause of acquired heart disease in children in the United states and Japan.
- Most commonly occurs in children younger than 5 years.
- Peaks between (2-3) years, and rare in children older than 7 years.
- Reoccur in 3% of cases.
- Peaks between February and May.

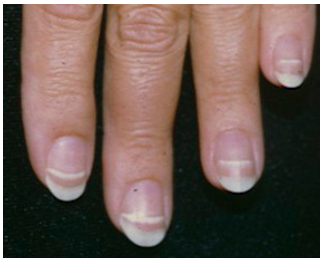
Clinical Manifestations

- Actually the disease has three phases as follows:

1. **Acute Phase:**
    - lasts (1-2) weeks
    - sudden onset of high fever >40 without an apparent cause
    - Fever is followed by: Conjunctival erythema (bilateral, bulbar, non-suppurative).
    - Mucosal changes including strawberry tongue.
    - Cervical lymphadenopathy >1.5 cm, seen in 70% of cases.
    - Swelling of hands and feet.
    - Rash, seen in 80% of cases, especially in the inguinal area and the chest.
    - Abdominal pain and hydrops of the gallbladder.
    - Cerebrospinal fluid pleocytosis, sterile pyuria, and arthritis particularly in medium-sized to large joints, may occur.
    - Carditis in the acute phase may be manifested by tachycardia, shortness of breath or overt congestive heart failure.

- Giant **coronary** artery aneurysms, which are rare but occur most commonly in young children, can appear during this phase.

2. **Subacute Phase:**
    - lasts until about the fourth week.
    - gradual resolution of fever (if untreated) and other symptoms.
    - Desquamation of the skin, particularly of the fingers and toes.
    - Platelet count increases to a significant degree often >1 million/mm3
    - Heralds the onset of coronary artery aneurysms.
3. **Convalescent Phase:**
    - Usually 6-8 weeks after the onset of illness.
    - Begins with the disappearance of clinical symptoms and continues until the ESR returns back to normal.
    - Beau lines of the finger nails may appear during this phase.



Risks for the Development of Coronary Artery Aneurysm

- Male gender
- Prolonged fever
- Prolonged elevation of inflammatory parameters such as ESR
- Age younger than 1 year and older than 6 years

Diagnosis

- The diagnosis of Kawasaki disease is based on the presence of **fever for more than 5 days without an identifiable source** and the presence of **four of five** of other criteria that will be listed below:

1. **Bilateral non-suppurative conjunctivitis**
2. One or more **changes of the mucus membranes of the upper respiratory tract**, including pharyngeal injection, injected lips and strawberry tongue.
3. One or more **changes of the extremities**, including peripheral erythema, peripheral edema, desquamation.
4. **Polymorphus rash, primarily truncal.**
5. **Cervical lymphadenopathy >1.5 cm in diameter.**

- The diagnosis of incomplete (atypical) KD:
    - Which occurs more commonly in infants, is made when **fever is present for at least 5 days even if only two or three clinical criteria are present**, particularly the presence of

coronary artery aneurysm.
    - KD should be considered in infants **younger than 6 months** of age with **fever for at least 7 days** even if no other criteria are present.

Other Symptoms & Signs

1. Respiratory: rhinorrhea, cough, pulmonary infiltrate
2. GI: diarrhea, vomiting, abdominal pain, hydrops of the gallbladder, jaundice
3. Neurologic: irritability, aseptic meningitis, facial palsy, hearing loss
4. Musculoskeletal: myositis, arthralgia, arthritis.

Differential Diagnosis

- **Infectious:**
    - Measles: maculopapular rash and redness of conjunctiva with fever, then Group A beta-hemolytic strep (causing scarlet fever).
    - Bacterial: Severe staph infection with toxin release
    - Viral: adenovirus, enterovirus, EBV, roseola
    - Spirocheteal: lyme disease, Leptospirosis
    - Parasitic: Toxoplasmosis
    - Rickettsial: Rocky mountain spotted fever, Typhus

- **Immunological/Allergic:**
    - Systemic juvenile rheumatoid arthritis
    - Atypical acute rheumatic fever
    - Hypersensitivity reactions
    - Stevens-Johnson syndrome which is erythema multiforme with involvement of the oral cavity.

Toxins

Mercury

Lab Results

In the acute stage there is:

- Leukocytosis
- Left shift
- Mild anemia
- Thrombocytopenia / thrombocytosis
- Elevated ESR, CRP
- Hypoalbuminemia
- Elevated transaminase (liver enzymes)
- Sterile pyuria

In the late stage:

- Thrombocytosis
- Elevated CRP

Cardiovascular Manifestations of Acute KD

- ECG changes:
    - Arrhythmias
    - Abnormal Q waves
    - Low voltage
    - ST-T wave changes
- CXR:
    - Cardiomegaly
- Suggestive of myocarditis:
    - Tachycardia, murmur
- Suggestive of pericarditis:
    - Present in 25% although symptoms are rare
    - Distant heart tones, pericardial friction rub, tamponade
- Echo findings:
    - Myocarditis with dysfunction
    - Pericarditis with an effusion
    - Valvar insufficiency
    - Coronary artery changes, which occurs in 15% to 25% of un treated patients and in 3-7% in those who are not treated of fever in the first 10 days with IVIG.

Regarding coronary aneurysms:

- The size varies in which it could be small =<5 mm diameter, medium 5-8mm, or giant >= 8 mm highest risk of sequelae (worst prognosis)
- The shape could be saccular or fusiform.
- 50% regress to normal by echocardiogram, 25% become smaller, and 25% don't regress.
- Approximately 50% of aneurysms resolve if they are:
    - Small size, fusiform morphology, female gender, age less than 1 year.

Cardiovascular sequelae:

- 0.3% mortality rate due to cardiovascular disease
- 10% from early myocarditis
- MI is principle cause of death in KD:
    i. 32% mortality
    ii. Most often in the first year
    iii. Majority while at rest/sleeping
    iv. About ⅓ are asymptomatic

Treatment

- **IVIG** is the mainstay of therapy for KD, although the mainstay of action is unknown. A single dose of IVIG (2g/kg over 12 hours) results in rapid resolution of clinical illness in most patients, and reduces the incidence of coronary artery aneurysms.
    - 10% does not respond, **what to do**? repeat the IVIG, if fever was still presenting after 36 hours of finishing the effusion.
- **Aspirin** is initially given as **anti-inflammatory dose** (80-100 mg/kg/day divided every 6 hours) in acute phase, once fever resolve aspirin is reduced to **anti-thrombotic doses** (3-5 mg/kg/day as a single dose) and given in the subacute and convalescent phases usually for 6-8 weeks until the follow up echocardiography documents the absence or resolution of coronary artery aneurysms.

Prognosis

- KD has an excellent prognosis
- **IVIG** reduces the prevalence of coronary artery disease from 20-25% in patients treated with aspirin alone to **2-4%** in patients treated with **IVIG and aspirin.**