Leishmaniasis

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General Information

- Caused by Leishmania parasite
- Transmitted to humans through bite of infected female sandflies (most common: phlebotomine sandfly)
- 3 main forms of leishmaniasis: Cutaneous, Mucocutaneous, Visceral
- Most individuals with leishmania parasite are asymptomatic but can still transmit disease
- Can be spread by: the bite of certain sandflies (common), blood/tissue transfusion (rare), organ transplant (rare), mother to baby (rare), sexually (rare)

Reservoir

- Dogs are the primary reservoir for the Leishmania parasite
- For some species of the parasite humans act as the main reservoir (L. donovani)
- No mammal is immune to carrying the Leishmania parasite, however some are more likely to serve as a reservoir than others (geographically dependent)

Leishmaniasis Life Cycle

- Infected Female Sandfly bite the skin ; injecting Leishmania promastigote into the skin
- Immune system responds, Neutrophils ingests the promastigote
    - Some parasites get destroyed, others are picked up by the immune cells
    - Most infections are asymptomatic & can lead to long lasting immunity
- Neutrophil act as trojan horse for the promastigote, Neutrophil engulfed by macrophage
- Promastigotes transform into amastigotes inside phagolysosomes ; survive as an intracellular parasite
- Continue replication inside macrophage till the cell bursts
- Amastigotes either infect new macrophages spreading to surrounding cells/tissues and organs or are picked up by another sand fly to continue the cycle

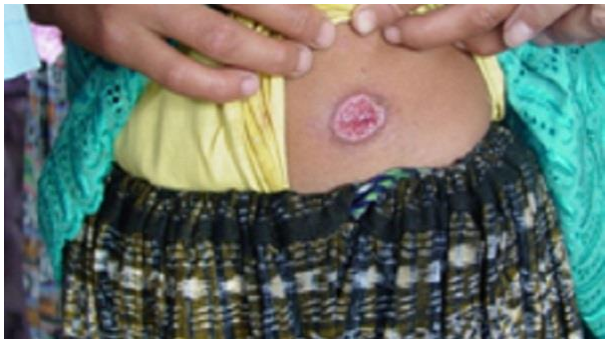
Immune System Response

- Two types of response, depending on the immune response determines outcome of leishmaniasis
    - Th1 (mainly type 1 helper T-cells and macrophages)
        - M1 macrophages prod. proinflammatory cytokine and chemokine
        - Mainly characterized by increased prod. of IFN-y & TFNα
        - Responds to IL-12
        - Resistant to Leshimania, promotes Th1 protective response
        - Control parasite replication & immunity against reinfection
        - Mismodulated Th1 can lead to severe tissue damage
    - Th2 (mainly type 2 helper T-cells & anti-infammatory signals)
        - Mainly characterized by nonstop inflammatory lesions
        - Responds to IL-4
        - Uncontrolled replication of parasite

        - Leading to spread of infection to the lymph nodes & spleen
- Immune response to Visceral leishmaniasis (VL)
    - Spreads to internal organs such as the spleen, liver, and bone marrow
    - Trigger swelling of the liver and spleen, immune-cell response to infection
        - As the infection spreads, triggers broad inflammatory response
    - Liver responds to inflammation by producing acute phase reactants
        - Proteins whose concentration in blood changes in response to inflammation
        - POS APR blood levels increase during inflammation, NEG APR blood levels decrease during inflammation ; Can change blood concentration, hemorrhage, etc.
    - VL behaves similar to bacterial sepsis ; causes high levels of inflammatory & anti-inflammatory signals in body
        - High levels of IL-10 & TGF-β (anti-inflammatory cytokines) allow VL to multiply easily
        - VL causes the immune system to overreact then shut down, making patients more vulnerable to bacterial infection (co-infection)
            - Patients with VL don't usually die from the common symptoms (fever, anemia, liver problems, etc.)
            - Cause of most death is severe inflammation & infection, patients with VL develop bacterial infection making the inflammation worse

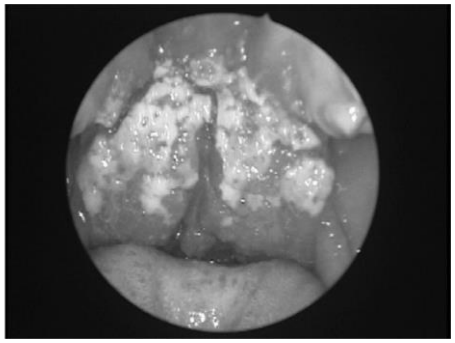
Types of Leishmaniasis & Symptoms

- Cutaneous Leshimaniasis (CL) ; common form of Leshimaniasis
    - Localized in the skin
    - Symptoms :
        - Skin sores ; affects skin & mucous membrane
            - Can leave life long scars
        - ulcers/erosion in the mouth, tongue, gums, lips, nose, and inner nose
        - Breathing difficulties
        - Swallowing difficulty
        - stuffy/runny nose & nosebleeds



- Mucosal Leshimaniasis (ML) ; severe form of CL

- Found in the nose & throat
- Symptoms :
    - Partial/total destruction of mucous membranes of the nose, mouth, and throat
        - Untreated can lead to severe destruction & disfigurement of the nose, mouth, and throat
    - Early symptoms :
        - Nose block & nose bleeding
        - Granulomas ; tiny clusters of white blood cells/tissues in the anterior nasal septum (depicted in picture above)



- Visceral Leshimaniasis (VL) ; uncommon of Leshimaniasis but most fatal
    - Found in spleen, liver, bone marrow, and lymph nodes
    - Symptoms :
        - Fever
        - Weight loss
        - Swelling of the spleen & liver
        - Abnormal blood tests ; low blood count (anaemia)
        - Vomiting
        - Diarrhea

Historical Notes

- Evidence of Leishmaniasis dates back to ancient Egypt, skeletal remains with signs of lesions consistent with cutaneous leishmaniasis
- Leishmania parasite causing visceral leishmaniasis discovered around 1900 by both William Leishman and Charles Donovan (individually) at the same time, lead to the naming of the specific parasite as *Leishmania donovani*

Treatment

- Species- and region-dependent
- Visceral and Mucocutaneous Leishmaniasis: should be treated
- Cutaneous Leishmaniasis: selective treatment
- Sterile cure is rarely achieved, even after treatment
- U.S. Medication Availability:
    - AmBisome®: intravenous; FDA-approved for Visceral Leismaniasis
    - Miltefosine: oral; FDA-approved for Visceral, Mucocutaneous, and Cutaneous Leishmaniasis (selected species; ≥12 yrs, ≥30 kg)
    - Other drugs available but not FDA-approved for leishmaniasis
- Vaccination:
    - Leishmaniasis is considered a vaccine-preventable disease because natural infection can induce strong protective immunity
    - Historically, people used ‘leishmanization,’ deliberately inoculating live parasites

to generate immunity
- Different types of vaccines are developing

Current Events

- Cutaneous Leishmaniasis in the U.S.
    - 41 novel U.S. cases 2007 - 2017; 59% endemic
    - Majority from Texas
    - All speciated cases: L. mexicana
    - Many patients had no travel history

- Estimation of a true global prevalence in 2023:
    - 0.6–1 million - cutaneous leishmaniasis
    - 530,000 - for visceral leishmaniasis
    - 4,627 visceral leishmaniasis deaths