Syphilis

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55 yo man presents to the ER with chest pain radiating to his back, shortness of breath and is found to have this on Chest CT:

19 yo man is seen at an STD clinic for a painless ulcer on his penis:

26 yo man presents to an ophthalmologist with progressive loss of vision in his Left eye, his fundoscopic exam looks like the picture on the left:

Mercutio: “… a pox on your houses!”
Romeo and Juliet, 1st Quarto, 1597, William Shakespeare

- 43 yo woman with RUQ pain is found to have a liver mass on U/S, biopsy of the mass reveals granulomas
- 26 yo man presents to the ED with new-onset seizures, a Head CT reveals an acute CVA
- 85 yo woman c/o shooting pains down her arms and in her face for 2 years duration
- 36 yo man presents to his PMD with an enlarging lymph node in his neck

Mercutio: “… a pox on your houses!”
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Origins of syphilis

- Pre-Colombian New World skeletal remains have bony lesions consistent with syphilis
- *T. pallidum* (cause of syphilis) and *T. pallidum pertunae* (cause of Yaws) have 100% genetic homology
- Native Americans suffered from syphilis (previously unknown to them) after Europeans arrived

Other names for syphilis

- Great pox
- Disease of Naples
- Italian pox
- French pox (Morbus gallicus)
- Turkish disease
- Spanish disease

Famous people who (probably) had syphilis

- Ivan the Terrible
- Henry VIII
- Cortes
- Francis I
- Charles Baudelaire
- Meriwether Lewis
- Friedrich Nietzsche
- Gaetano Donizetti
- Toulouse Lautrec
- Al Capone
- ...

Galen’s humors

- Pox diseases were associated with phlegm (one of the four humors)
- Treatments should promote spitting and sweating

The Great Pox – Syphilis in the 1500s

From Epidemics and History: Disease, Power and Imperialism by Sheldon Watts, Yale University Press 1999

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Treating syphilis in the 1600s

Other treatments

- Mercury
  - Given until patient produced copious saliva
  - Sign of mercury poisoning: copious saliva
- Arsenic
  - Arsphenamine®, Salvarsan®
- Bismuth (i.e. Pepto-Bismol)
- Fever therapy
- Malaria therapy
- Penicillin --- more on this later

Syphilis in wartime

- World War I
  - Syphilis most common cause for rejection from service
  - Up to 10% of European theater allied soldiers had syphilis
- World War II
  - Most penicillin available was used not to treat infected wounds but to treat syphilis (so that soldiers could return to the front)

Syphilis and sin in the 19th century

Treponemes

- Family Spirochaetaceae
  - Borrelia
    - Lyme disease, Tick-borne and louse borne relapsing fever
  - Leptospira
  - Treponema
    - Treponema pallidum subsp. pertenue
    - Treponema pallidum subsp. endemicum
    - Treponema pallidum subsp. carateum
    - Treponema pallidum subsp. pallidum
      - syphilis
Map of endemic treponemal diseases

Yaws: *Treponema pertenue*

Treponema pallidum subsp. pallidum
- Slender, tightly coiled, helical
- Undulating movement about its center (flexuose) distinguish it from nonpathogenic treponemes on darkfield microscopy
- Cannot be cultured in vitro
  - Rabbits
- Unlike other pathogenic bacteria, genome lacks apparent transposable elements
  - PCN sensitivity
  - Paucity of genes involved in biosynthesis of nutrients or energy production: scavenger

Bejel: *Treponema endemicum*

Darkfield microscopy
World Health Organization estimates, new adult cases 1999

- 100,000 North America
- 140,000 western Europe
- 100,000 eastern Europe
- 100,000 central Asia
- 370,000 in north Africa and the Middle East
- 3–4 million each in
  - Latin America
  - the Caribbean
  - sub-Saharan Africa
  - south and southeast Asia

Specific populations

- MSM
  - The CDC estimates that in 2004, approximately 64 percent of all cases of primary and secondary syphilis were in MSM.
- HIV
  - Among the 6862 cases of primary and secondary syphilis documented in 2002 by the CDC, 25 percent occurred in persons co-infected with HIV
  - the risk group with the highest incidence rates were HIV-infected MSM

Epidemiology

- Early syphilis is reportable
- Mini-epidemic in the US in the late 80s to early 90s
  - case rates that were higher than at any time since the introduction of penicillin

Definitions

- Disease stages
  - Early (<1 year since infection), more likely to be infectious
    - Primary
    - Secondary
    - Early latent
  - Late latent (>1 year since infection, or unknown duration), less infectious but more difficult to treat
    - A.k.a. tertiary syphilis

Syphilis incidence in the US

- Oslo, Norway
  - 1400 patients with syphilis in the late 19th century, untreated
    - 10 percent developed cardiovascular syphilis
    - 16 percent developed gummatous syphilis
    - 6.5 percent developed symptomatic neurosyphilis
Natural History (2)

- Tuskegee, Macon County, Alabama
  - 431 black men with syphilis between 1932 and 1972, untreated
  - PCN discovered in 1947, not offered
  - 1972: news stories and public outcry, study closed
  - 1974:
    - National Research Act was signed into law
      - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
    - Legislation passed that required researchers to get voluntary informed consent from all persons taking part in studies done or funded by the Department of Health, Education, and Welfare (DHEW).
      - They also required that all DHEW-supported studies using human subjects be reviewed by Institutional Review Boards
    - 1979 Belmont Report
      - Respect for Persons
      - Beneficence
      - Justice
  - 1979 Belmont Report
  - 1979 Belmont Report

Transmission

- Transmission of *Treponema pallidum* usually occurs via direct contact with an infectious lesion during sex.
  - The spirochete gains access via disrupted epithelium at sites of minor trauma.
- Early lesions are all very infectious
  - Chancres
  - Mucous patches
  - Condyloma lata
- It has been estimated that transmission occurs in approximately one-third of patients exposed to these lesions.
  - Need as few as 60 organisms to infect

Clinical manifestations

- Primary syphilis
  - Incubation
    - Median 21 days (range 3 to 90 days)
  - Papule develops into classic chancre lesion at the site of inoculation
    - Clean based ulcer
    - Indurated and painful
    - Heals spontaneously in 3-6 wks
    - Wide dissemination of spirochete occurs

Penile ulcer

- Early pathophysiology
  - Infection initiated when *T. pallidum* gains access to subcutaneous tissues via microscopic abrasions
  - Evades early host immune responses and establishes the initial ulcerative lesion
    - Some organisms establish infection in regional draining lymph nodes
  - Widespread dissemination of spirochetes despite apparent effective immune control (i.e., resolution of chancre)
  - Early lesional infiltration of PMNs replaced by T lymphocytes
    - Secondary syphilitic lesional fluid is enriched for CD4+ and CD8+ T cells and dendritic cells
      - Many of these dendritic cells also expressed HIV coreceptors (eg, CCR5)
  - Humoral immune responses lead to the development of a variety of antibodies that can be detected relatively early in the course of syphilis.
Clinical manifestations secondary syphilis - 1

- Systemic illness a few months after chancre
  - Rash
    - Any type except vesicular
    - Classically is symmetric macular or papular
    - discrete red or reddish-brown lesions 0.5 to 2 cm in diameter
  - Palms and soles involvement is an important clue to the diagnosis of secondary syphilis.

Rash of secondary syphilis

- Other rashes
  - Condyloma lata
  - Mucous patches
- Systemic symptoms
- Lymphadenopathy
- Alopecia
- Protean manifestations
  - Hepatitis
  - GI, MS, Renal abnormalities
  - Neurologic manifestations
  - Ocular manifestations

Mucous patches

Condyloma lata

Pathology of secondary syphilis skin lesions
Pathology of secondary syphilis skin lesions

Clinical manifestations of late syphilis

- Gummatous syphilis
  - The Great pox (as opposed to the small pox)
  - Uncommon nowadays
- Cardiovascular syphilis
  - ascending thoracic aorta resulting in a dilated aorta and aortic valve regurgitation
- Syphilis of the CNS

Lymphadenopathy

Hepatic granulomas

Alopecia

Syphilitic aortitis
Diagnosis of primary syphilis

- Darkfield microscopy of chancre scraping
  - Corkscrew-shaped organisms with tightly wound spirals
  - Forward and backward motion with rotation
  - Soft side-to-side bending and twisting
  - Specific but not sensitive
- Direct fluorescent antibody test of specimen (DFA-TP)
  - Not widely used

Diagnosis of syphilis

- Serologic tests
  - Non-treponemal
    - Venereal Disease Research Laboratory (VDRL) test (less commonly used except on CSF)
    - Rapid Plasma Reagin (RPR) test
      - Tests for auto-antibodies to cardiolipin, a tissue lipid
      - Easy and cheap, used for screening
      - Reported as a titer
      - Used to follow treatment
      - Sensitive except in late syphilis, specific
  - Treponemal
    - Fluorescent treponemal antibody absorption (FTA-ABS) test
    - Microhemagglutination test for antibodies to Treponema pallidum (MHA-TP)
    - Treponema pallidum particle agglutination assay (TPPA)
      - More sensitive and more specific, even in late syphilis
      - Reported as positive or negative

Gold Standard:
- Culture of *T. pallidum* by *in vivo* intratesticular inoculation of rabbits
- Not done routinely

RPR

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive control serum</th>
<th>Negative control serum</th>
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<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
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Darkfield microscopy
Time course of antibody development during syphilis

Specificity
- Acute false positives non-treponemal test
  - Pneumococcal pneumonia, TB, HIV, Measles
  Infectious mononucleosis, Viral hepatitis,
  Pregnancy...
- Chronic false positive non-treponemal test
  - Chronic liver disease, Malignancy, Injection drug use,
  Connective tissue disease...
- False positive treponemal test
  - Lyme borreliosis, Malaria, Infectious mononucleosis,
  Leptospirosis, Systemic lupus erythematos...

Screening for syphilis
- Risk factors
  - MSM who engage in high risk behaviors
  - CSWs
  - persons who exchange sex for drugs
  - adult correctional facilities
- Two step process
  - Non-treponemal test followed by a
  confirmatory treponemal test if positive

Other antibiotics
- Doxycycline
- Azithromycin
- Ceftriaxone

Treatment - 1
- Prolonged antibiotics necessary since *T. pallidum* divides slowly
  - one doubling in vivo per day
- Long-acting preparations
- Highly sensitive to penicillin

Treatment - 2
- Early syphilis
  - Benzathine penicillin G 2.4 million units
    intramuscularly x 1
- Late latent syphilis or latent syphilis of
  unknown duration
  - Benzathine penicillin G 2.4 million units
    intramuscularly every week for 3 weeks
Jarisch-Herxheimer reaction

- acute febrile reaction during first 24 hrs of therapy
- headache and myalgias
- most common among patients with early syphilis
- antipyretics can be used for symptomatic treatment

Neurosyphilis (1)

- Examine CSF if:
  - latent syphilis and any of the following
    - Ophthalmic signs or symptoms
    - Evidence of active tertiary syphilis
    - Treatment failure (including failure of nontreponemal tests to fall appropriately)
    - HIV infection with late latent syphilis or syphilis of unknown duration

Neurosyphilis (2)

- CSF analysis:
  - cell count
  - protein concentration
  - CSF-VDRL titer
- Expect:
  - moderate mononuclear pleocytosis
  - elevated protein concentration
  - Positive CSF-VDRL
    - very specific, not sensitive

Neurosyphilis (3)

- Early
  - Transient or persistent asymptomatic meningitis
- Early symptomatic (weeks to years)
  - Symptomatic meningitis
  - Ocular findings
  - Stroke
- Late symptomatic meningitis (years to decades)
  - Paralysis
  - Dementia
  - Personality change
  - Tabes Dorsalis

Monitoring the response to treatment

- Monitor changes in the titer of reagin antibodies
  - Use the same testing method (eg, RPR or VDRL)
- Patients with primary and secondary syphilis:
  - Expect a fourfold decline by six months
  - Expect an eightfold decline by 12 months
- Slower rate of decline among patients with early latent syphilis
  - Expect fourfold decline by 12 months
- If expected change does not occur, test for HIV

Neurosyphilis (4)

- Early
  - Transient or persistent asymptomatic meningitis
- Early symptomatic (weeks to years)
  - Symptomatic meningitis
  - Ocular findings
  - Stroke
- Late symptomatic meningitis (years to decades)
  - Paralysis
  - Dementia
  - Personality change
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Tabes dorsalis

- Less common in antibiotic era
- Disease of the posterior columns of the spinal cord and of the dorsal roots
- Ataxia and lancinating pains
- Pupillary irregularities
  - Argyll-Robertson pupil
    - small
    - does not respond to light
    - contracts normally to accommodation and convergence
    - dilates imperfectly to mydriatics
    - dilate in response to painful stimuli.
Neurosyphilis (4)

- Treatment
  - Penicillin G 3 to 4 million units IV every four hours or 24 million units continuous IV infusion for 10 to 14 days
  - Neurologic examination and lumbar puncture
    - three to six months after treatment
    - every six months thereafter
  - CSF WBC count should normalize and CSF VDRL should become nonreactive by 2 years after treatment
  - Failure to respond or a worsening of CSF WBC should prompt re-treatment.

Syphilis in pregnancy

- Sequelae of congenital infection
  - Perinatal death
  - Premature delivery
  - Low birth weight
  - Congenital anomalies
  - Active congenital syphilis in the neonate

“He who knows syphilis, knows medicine”
-Sir William Osler

Syphilis serology in HIV

- More false positive non-treponemal tests
- Higher non-treponemal titers than non-HIV infected
- Loss of reactivity in late HIV disease
- Slower decline of titers on treatment