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:

- 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!”

Romeo and Juliet, 1st Quarto, 1597, William Shakespeare
Origins of syphilis

- Pre-Colombian New World skeletal remains have bony lesions consistent with syphilis
- *T. pallidum 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

- Pope Alexander VI
- 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

Galen’s humors

- Pox diseases were associated with phlegm (one of the four humors)
- Treatments should promote spitting and sweating
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
      - yaws
    - Treponema pallidum subsp. endemicum
      - bejel, endemic syphilis
    - Treponema pallidum subsp. carateum
      - pinta
    - Treponema pallidum subsp. pallidum
      - syphilis
**Map of endemic treponemal diseases**

**Pinta: Treponema carateum**

**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

Natural History (1)

- 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

Syphilis incidence in the US

- Graph showing the incidence of syphilis in the US from 1970 to 2000, with a focus on the period 1998 to 2004.
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

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
  - Chancre
  - 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 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.

Clinical manifestations primary syphilis

- Incubation
  - Median 21 days (range 3 to 90 days)
- Primary syphilis
  - Papule develops into classic chancre lesion at the site of inoculation
    - Clean based ulcer
    - Indurated and painless
    - Heals spontaneously in 3-6 wks
  - Wide dissemination of spirochete occurs
Clinical manifestations secondary syphilis - 2

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

Lymphadenopathy

Mucous patches

Alopecia

Condyloma lata

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
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

Diagnosis of syphilis

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

Diagnosis of syphilis

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<tr>
<th>RPR</th>
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<td>Negative control serum</td>
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<td>Test</td>
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<td>positive</td>
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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 erythematosus...

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

Treatment - 1

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

Other antibiotics

- Doxycycline
- Azithromycin
- Ceftriaxone

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 (2)

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

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
如果 expected change does not occur, test for HIV

Neurosyphilis (3)

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

★ 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

Tabes dorsalis

(aka locomotor ataxia)

- 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.

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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.

“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

Syphilis in pregnancy

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