Syphilis

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Overview

- Definition
  - Systemic infection caused by the spirochete bacteria *Treponema pallidum*
  - Often transmitted through sexual activity, but may be congenital
  - The "Great Imitator" – may cause morbidity to any of the major body organs and can mimic a great variety of disease
- Symptoms
  - Blurring
  - Redness
  - Pain
  - Light sensitivity
  - Floaters
  - Scotoma
  - Usually present without systemic sign of syphilis
- Laterality
  - Bilateral 44–71%
- Course
  - Progressive
- Age of onset
  - Reproductive age but may present in childhood if congenital infection
- Gender/race
  - M > F; higher rates among men who have sex with men
- Systemic association
  - Multisystemic involvement presenting in stages when untreated
  - Considered neurosyphilis when uveitis is present

C. S. Foster et al. (eds.), *Uveitis*, https://doi.org/10.1007/978-3-030-52974-1_26

Exam: Ocular

- Ocular syphilis may occur at any stage of syphilis

Anterior Segment

- More common
  - Anterior uveitis
    More commonly present with vitritis than isolated
    Granulomatous or nongranulomatous
  - Interstitial keratitis
  - Posterior synechiae
  - Iris atrophy
- Less common
  - Lens dislocation
  - Chancre at conjunctiva or eyelid in primary syphilis
  - Iris engorgement – "roseola" – middle third iris involvement (rare)

Posterior Segment

- Chorioretinitis focal/diffuse
  - Most common posterior segment involvement
  - Multifocal typically grayish-yellow lesions:
    Typically posterior pole or near equator
  - Serous RD, disc edema, vasculitis, and vitritis are occasionally associated signs
  - *Acute syphilitic posterior placoid chorioretinitis (ASPPC)* (rare, but characteristic)
    One or more large, yellowish, circular, or oval placoid lesions at the level of RPE in or near macular
- Retinitis without choroidal involvement/necrotizing retinitis
- Vasculitis +/− vitritis
- Intermediate uveitis
- Panuveitis
- Neuroretinitis
- Benign tertiary syphilis (Gumma): in choroid and iris (rare)

Exam: Systemic

- *Untreated* syphilis may progress to four stages:
  1. Primary syphilis: *Chancre*
     - Appears ~3 weeks after infection and resolves without treatment ~4 weeks after appearance

  - Painless indurated ulcer at genitalia/mouth/skin/conjunctiva or eyelid
2. Secondary syphilis: *Generalized rash, mucocutaneous lesion, and lymphadenopathy*
  - 4–10 weeks after the initial manifestation
  - Maculopapular rash; prominent on the palms and soles
  - Flu-like symptoms, nausea, hair loss, mouth ulcers, and joint pains
  - Self-resolves in several weeks
3. Latent stage: *No clinical manifestation is detectable*
  - Noncontagious
  - Can last in this stage for entire lifetime
    3.1 Early latent (up to 1 year after initial infection)
    3.2 Late latent (after 1 year)
4. Tertiary syphilis: represents an *obliterative endarteritis*
  - Can appear 10–30 years after infection
  - Risk of severe morbidity and mortality
    4.1 Benign tertiary syphilis (Gumma): in the skin and mucous membranes
    4.2 Cardiovascular syphilis: aortitis, aortic aneurysm, aortic valve insufficiency
    4.3 Late-stage neurosyphilis: general paresis and tabes dorsalis

- Neurosyphilis
  - Can occur at any stage of syphilis
  - Cranial nerve dysfunction, stroke, meningitis, seizure, neuropsychiatric, general paresis, and tabes dorsalis

Imaging

- OCT
  - CME, retinal atrophy
  - ASPPC: subretinal fluid, ellipsoid zone disruption, and hyperreflective granular RPE changes
- FA
  - Nonspecific vasculitis: vascular and disc staining, pericapillary leakage
  - ASPPC: Hypofluorescent central lesion in the early phase with leopard spotting (scattered hypofluorescence) and progressive hyperfluorescence in mid-late phase; late leakage from the optic disc
- ICG
  - ASPPC: hypofluorescence corresponding to the macular lesion in both the early and late phases

Laboratory and Radiographic Testing

- Syphilis testing is warranted in *all patients* with uveitis of unknown etiology (Table 26.1)

Table 26.1 Interpretations of syphilis tests

Nontreponemal	Treponemal assays	Interpretation	Further action
Reactive ≥ 1:8.	Reactive.	Current syphilis infection	Clinical evaluation should be performed to identify signs, symptoms, or past history of infection.
Reactive at 1:1, 1:2, or 1:4.	Reactive.	Current or past infection, or due to serofast condition	
Reactive ≥ 1:8.	Nonreactive.	Inconclusive for infection, biological false positive likely	Clinical evaluation should be performed to identify signs, symptoms, or past history of infection. If recent exposure is suspected, redraw sample in 2–4 weeks.
Reactive at 1:1, 1:2, or 1:4.	Nonreactive.	Syphilis infection unlikely, biological false positive likely	
Weakly reactive, Prozone has been ruled out.	Nonreactive.	Syphilis infection unlikely	
Weakly reactive, Prozone has been ruled out.	Reactive.	Past or potential early syphilis infection	
Nonreactive.	Reactive: False positive of treponemal assays has been ruled out by repeating with different methods.	Past or potential early syphilis infection	If past history of treatment is reported, no further management is needed unless recent exposure suspected → redraw sample in 2–4 weeks.

Adapted from Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serology Testing. December 2015

- Confirm diagnosis with multiple tests via at least one treponemal-specific *and* nonspecific method:
  1. Nontreponemal tests
     - RPR/VDRL
     - Quantify amount of antibody against *nontreponemal antigens*, such as cardiolipin, which is released by host cells infected by *T. pallidum*
     - "Nonreactive" or "reactive" at dilutions titer (e.g., 1:2, 1:4, 1:32)
     - Titers decrease and become negative after treatment → *use to monitor response to therapy*
     - VDRL false negative 30% in latent syphilis, while FTA-ABS only 1–2%
  2. Treponemal tests
     - FTA-ABS
     - TP-PA/TPHA/MHA-TP
     - Immunoassay (EIA/CIA): Treponemal IgG, IgM
       - Confirmatory test
       - Remains positive for lifetime, regardless of treatment status
       - More sensitive than nonspecific serologic test during latent stage
- Direct detection of pathogen from various bodily fluids

  - Dark-field microscopy
  - PCR
- CSF analysis performed in *every* case of syphilitic uveitis
- HIV checked in *all* syphilis patients
- Reliability of testing
  - False positive
    RPR/VDRL
    - Transient (6 months or less) – malaria, mycobacterial disease, HIV, vaccination
    - Long-lasting (greater than 6 months) – SLE, RA, biliary cirrhosis, old age

    FTA-ABS
    - SLE, RA, biliary cirrhosis, old age
  - False negative
    Latent syphilis, VDRL false negative 30% while only 1–2% in FTA-ABS
    Prozone phenomenon
    - Results in negative or weakly positive nontreponemal test
    - No agglutination occurs due to antibody excess, mostly in primary and secondary syphilis → *dilute and retest*
  - Serofast
    Persistent nontreponemal titer after treatment
    Consider persistent infection (? CNS)/retreating when nontreponemal titers do not decrease fourfold within 6 months after treatment

Differential Diagnosis

- Syphilis should be in the differential diagnosis for every uveitis patient

Treatment

- With uveitis, treat as neurosyphilis, regardless of CSF result
  - Intravenous penicillin G 18–24 million unit per day (3–4 million units IV q4h or continuous infusion) for 10–14 days
  - Alternative – Procaine penicillin 2.4 million units IM once daily plus Probenecid 500 mg orally QID, both for 10–14 days
    Ensure compliance
  - Follow nontreponemal titer q6 months
- Supplemental therapy, when needed
  - IM benzathine penicillin G 2.4 million units weekly up to 3 weeks
    To provide comparable total duration of therapy to late syphilis
- Penicillin-allergic patients
  - Ceftriaxone 2 g daily either IM or IV for 10–14 days (beware cross-reaction)
  - Tetracycline hydrochloride 500 mg PO QID for 30 days

  - Doxycycline 100 mg BID for 14 days
  - Macrolide (clarithromycin)
  - Consider penicillin desensitization
- Jarisch-Herxheimer reaction
  - Hypersensitivity reaction to treponemal antigens, released in large numbers as spirochetes are killed during therapy
  - Usually in the first 24 hours during the initial infusion treatment
  - Fever, myalgia, and headache ± increase ocular inflammation
  - Supportive treatment: antipyretics, NSAID
  - Local and systemic corticosteroid, with severe ocular inflammation

Referral/Comanagement

- Infectious disease