SYPHILIS EDUCATION TODAY
Syphilis the “Great Imitator”
Fascinating Cases with a Focus on Dermatological Manifestations

Jeffrey D. Klausner, MD, MPH
Director, STD Prevention and Control Services
San Francisco Department of Public Health
Associate Clinical Professor of Medicine,
Divisions of AIDS and Infectious Diseases
University of California, San Francisco

Kenneth A. Katz, MD, MSc, MSCE
Epidemic Intelligence Service
CDC, STD Prevention and Control Services
San Francisco Department of Public Health

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Dermatological Manifestations of Syphilis

Kenneth A. Katz, MD, MSc, MSCE
Epidemic Intelligence Services
Centers for Disease Control and Prevention
STD Prevention and Control Section
San Francisco Department of Public Health
Disclosure

None
Primary syphilis

- **Chancre:** Localized infection at site of inoculation
- Appears on average 21 days after exposure (range, 10-90 days)
- Genitals, lips, tongue, tonsil, breast, index finger, anus
- Indurated (hard) papule
- Usually painless
- May have lymphadenopathy
- Typically single, may be multiple
- Heals spontaneously in 1-4 months
- Serology may be negative in early infection (“prozone”)
Primary syphilis – differential diagnosis

• Other ulcerative STDs
  – Herpes
  – Chancroid
  – Lymphogranuloma venereum
  – Donovanosis (granuloma inguinale)

• Other infectious causes
  – Abscess/furuncle

• Trauma

• Aphthous ulcer

• Fixed drug eruption
Primary syphilis -- differential

Herpes

Grouped vesicles on an erythematous (red) base
Primary syphilis --
differential

Herpes

Vesicles may rupture, leaving “punched out” erosions (areas missing the top layer of the skin)
Primary syphilis -- differential

Herpes

Grouped erosions with exudate (discharge) on vulva
Primary syphilis -- differential

Herpes

More subtle presentation in recurrent disease
- May be less painful
- Patient may not be aware of outbreak
Primary syphilis -- differential

Chancroid
Primary syphilis -- differential

Chancroid

http://dermatology.cdlib.org/127/case_reports/inguinale/khachemoune.html
Primary syphilis -- differential

Lymphogranuloma venereum

http://tmcr.usuhs.mil/tmcr/chapter20/epidemiology.htm
Primary syphilis -- differential

Abscess/Furuncle
Primary syphilis -- differential

Aphthous ulcer
Primary syphilis -- differential

Fixed drug eruption
Secondary syphilis

- Skin manifestations ("syphilids") in 80%
- 6-8 weeks after chancre appears
  - May overlap chancre or appear after chancre heals
- First macules (flat), may be itchy
- Then firm papules (raised)
Secondary syphilis

- Palmar and plantar involvement is typical
- Firm papules may be tender
Secondary syphilis

• Condyloma lata
  – Soft, red, mushroom-like mass with a smooth, moist surface
Secondary syphilis

Mucous patches
Secondary syphilis

• Annular papules and plaques
  – “Nickels and dimes”
  – More common in African Americans
Secondary syphilis

- Alopecia (hair loss)
  - “Moth-eaten” pattern
  - Non-scarring

www.merckmedicus.com
Secondary syphilis – differential diagnosis

• Infectious
  – Tinea versicolor
  – Tinea corporis
  – Pityriasis rosea (? Infectious)
  – Viral exanthem
  – Erythema multiforme
  – Condyloma acuminatum

• Others
  – Drug eruptions
    • Morbiliform
  – Psoriasis
Differential diagnosis of secondary syphilis

Tinea versicolor – mycology.adelaide.edu.au
Differential diagnosis of secondary syphilis

Tinea corporis
Differential diagnosis of secondary syphilis

KOH Preparations

Tinea versicolor:
“Spaghetti and meatballs”

Tinea corporis:
Branching hyphae
Differential diagnosis of secondary syphilis

Pityriasis rosea with herald patch – www.dermatlas.jhmi.med.edu
Differential diagnosis of secondary syphilis

Viral exanthem
Differential diagnosis of secondary syphilis

Erythema multiforme
Drug rashes: Erythema multiforme (EM)
Drug rashes: Erythema multiforme (EM)

• Causes
  – Drugs
    • Sulfonamides, penicillin, phenytoin, barbiturates, phenylbutazone, allopurinol
  – Infections
    • Herpes simplex, Mycoplasma
  – Idiopathic (>50%)

• Clinical
  – May have history of EM
  – Lesions evolve over several days
  – May be pruritic or painful
  – Macules → papules → vesicles and bullae
  – Dull red
  – Iris or target-like lesions typical
  – Localized to hands, face, or generalized
  – Mucous membrane involvement – may be painful, tender
  – Mouth lesions may be painful, tender
  – Fever, weakness, malaise may occur
Palmoplantar lesions

- Secondary syphilis
- Erythema multiforme
- Reactive arthritis
- Rocky Mountain Spotted Fever
- Embolic disease
- Disseminated gonococcal/meningococcal infection
- Hidradenitis
- Psoriasis
- Mycosis fungoides (CTCL)
Differential diagnosis of secondary syphilis

Condyloma acuminatum
Differential diagnosis of secondary syphilis

Morbilliform drug eruption – missinglink.ucsf.edu
Drug rashes: Exanthematous eruptions

- Can occur with nearly any drug
- Usually within < 14 days after start (range, 1-21 days)
- Earlier onset after rechallenge with sensitizing drug
- High probability drugs (3-5%)
  - Penicillin and related antibiotics, carbamazepine, allopurinol, gold salts
- Medium probability:
  - Sulfonamides, erythromycin, NSAIDs, hydantoin derivatives, isoniazid, chloramphenicol, streptomycin
- Low probability (≤1%)
  - Tetracyclines, Barbiturates, benzodiazepines, phenothiazines
- HIV-infected individuals: 50-60% on sulfa drugs (e.g., Septra)
- Cross reactivity
  - 10% of penicillin → cephalosporins
  - 20% sulfa
Drug rashes: Exanthematous eruptions

Clinical
- Macules and/or papules
  - Few millimeters to 1 cm
  - Bright red
  - Typically starts on chest
- Purpura may be present on lower leg lesions
- May progress to generalized exfoliative dermatitis
- May be pruritic
- Fever, chills may be present

Differential diagnosis
- Viral exanthem (face → trunk), secondary syphilis, pityriasis rosea, contact dermatitis

Management
- Discontinue (but may “treat through” – e.g., Atripla), antihistamine, corticosteroids
Differential diagnosis of secondary syphilis

Psoriasis
Differential diagnosis of secondary syphilis

Psoriasis
Differential diagnosis of secondary syphilis

Psoriasis

www.dartmouth.edu
Tertiary syphilis

- 3-5 years after infection begins
- Nodular syphilids or gummas
Pearl – Differential diagnosis of genital ulcer disease

- **STDs**
  - Herpes (HSV-2 and HSV-1)
  - Syphilis (primary)
  - Chancroid
  - LGV
  - Granuloma inguinale

- **Non-STDs**
  - Infectious
    - Candidiasis/balanitis
    - Scabies
    - Impetigo
  - Non-infectious
    - Aphthous ulcers
    - Behcet’s syndrome
    - Trauma
    - Neoplasia (e.g., squamous cell carcinoma)
    - Drug-related
      - Fixed drug eruption
      - Erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis
# Pearl – Differential diagnosis of genital dermatoses

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Erosion/Ulcer</th>
<th>Color Change</th>
<th>Adenopathy</th>
<th>Other Characteristics of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD</td>
<td>Syphilis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Indurated, painless</td>
</tr>
<tr>
<td></td>
<td>Herpes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Multiple, painful</td>
</tr>
<tr>
<td></td>
<td>Chancroid</td>
<td>Yes</td>
<td>No</td>
<td>Yes (may rupture)</td>
<td>Kissing lesions</td>
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<tr>
<td></td>
<td>Genital warts</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Verrucous papules</td>
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<tr>
<td></td>
<td>Granuloma inguinale</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Friable, painless</td>
</tr>
<tr>
<td></td>
<td>Molluscum contagiosum</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Papules</td>
</tr>
<tr>
<td></td>
<td>Amebiasis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Painful</td>
</tr>
<tr>
<td></td>
<td>Scabies</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Pruritic papules</td>
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<tr>
<td>Non-STD infection</td>
<td>Candida</td>
<td>Superficial</td>
<td>Bright red</td>
<td>No</td>
<td>Satellite pustules</td>
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<tr>
<td></td>
<td>Tinea cruris</td>
<td>No</td>
<td>Red-pink</td>
<td>No</td>
<td>Annular scaling</td>
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<tr>
<td>Inflammatory</td>
<td>Psoriasis and seborrhea</td>
<td>No</td>
<td>Red-pink</td>
<td>No</td>
<td>Confluent fine scaling</td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
<td>Yes (female); no (male)</td>
<td>Red/white; purple</td>
<td>No</td>
<td>Erosion (female), painful; plaque (male)</td>
</tr>
<tr>
<td></td>
<td>Lichen sclerosus et atrophicus</td>
<td>Rarely</td>
<td>Bone white</td>
<td>No</td>
<td>Ecchymoses itch/burn</td>
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<tr>
<td>Autoimmune</td>
<td>Vitiligo</td>
<td>No</td>
<td>Bone white</td>
<td>No</td>
<td>Asymptomatic</td>
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<tr>
<td>Multisystem</td>
<td>Behget syndrome</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Punched-out ulcers</td>
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<tr>
<td></td>
<td>Reiter syndrome</td>
<td>Superficial</td>
<td>No</td>
<td>No</td>
<td>Scaly plaques</td>
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<tr>
<td></td>
<td>Crohn disease</td>
<td>Yes, linear</td>
<td>No</td>
<td>No</td>
<td>Crural creases, purulent oozing</td>
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<tr>
<td>Exogenous</td>
<td>Contact dermatitis</td>
<td>Superficial, if any</td>
<td>Red</td>
<td>No</td>
<td>Blister, edema, itching</td>
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<tr>
<td></td>
<td>Corticosteroid abuse</td>
<td>No (atrophic)</td>
<td>Bright red</td>
<td>No</td>
<td>Burning</td>
</tr>
<tr>
<td></td>
<td>Genital bite</td>
<td>Yes, deep</td>
<td>No</td>
<td>No</td>
<td>Rapid spread, painful</td>
</tr>
<tr>
<td></td>
<td>Fixed-drug eruption</td>
<td>Superficial</td>
<td>Purple-red</td>
<td>No</td>
<td>Circular shape</td>
</tr>
<tr>
<td></td>
<td>Factitious</td>
<td>Often</td>
<td>No</td>
<td>No</td>
<td>Bizarre shape</td>
</tr>
<tr>
<td>Tumor</td>
<td>Extramammary Paget syndrome</td>
<td>No</td>
<td>Red</td>
<td>Maybe</td>
<td>Scaling, multifocal</td>
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<tr>
<td></td>
<td>SCC in situ</td>
<td>Superficial, if any</td>
<td>Red, velvety</td>
<td>No</td>
<td>May be multifocal</td>
</tr>
<tr>
<td></td>
<td>SCC invasive</td>
<td>Maybe</td>
<td>Red-pink</td>
<td>Maybe</td>
<td>Hard nodule</td>
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<tr>
<td></td>
<td>Genital melanosis</td>
<td>No</td>
<td>Brown-black</td>
<td>No</td>
<td>Multiple small macules</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>May</td>
<td>Brown-black</td>
<td>Maybe</td>
<td>Hard nodule</td>
</tr>
</tbody>
</table>

Abbreviations: SCC, squamous cell carcinoma; STD, sexually transmitted disease.

*Kissing lesions are lesions appearing on adjacent skin areas and fixed-drug eruption is recurring lesion at same site each time offending drug administered.*
Questions?

Ask Dr. Katz


http://msnbcmedia4.msn.com/j/msnbc/Component/Photos/061227/061227_penisCartoons_vmed_5p%20copy.widec.jpg
Biology, Epidemiology, and Fascinating Cases

Jeffrey D. Klausner, MD, MPH
Director, STD Prevention and Control Services
San Francisco Department of Public Health
Associate Clinical Professor of Medicine,
Divisions of AIDS and Infectious Diseases
University of California, San Francisco
Disclosure

• Dr. Klausner is an employee of the City & County of San Francisco and a Faculty member of the University of California, San Francisco

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• Communications Strategies, Inc., CSI Medical Education and King Pharmaceuticals, Inc. supported Dr. Klausner to conduct various educational programs
Syphilis Biology

- *Treponema pallidum* a spirochete bacterium spread through sexual contact—oral, anal or vaginal sex
- Humans only host
- Facilitates HIV transmission

San Francisco City Clinic Web site [www.dph.sf.ca.us/sfcityclinic/stdbasics/syphilis.asp](http://www.dph.sf.ca.us/sfcityclinic/stdbasics/syphilis.asp)
Primary and Secondary Syphilis Rates by Sex, United States, 1990–2007*

Rate (per 100,000 men/women)

* 2007 data are preliminary

Hillard Weinstock, Division of STD Prevention, CDC, Presentation at STD National Conference, March 11, 2008
Primary and Secondary Syphilis: Rates by Race and Ethnicity, 1997–2007*

Rate (per 100,000 population)

- African-American
- White
- Hispanic
- Asian/PI
- Am. Indian

* 2007 data are preliminary
Congenital Syphilis — Reported Cases for Infants <1 Year of Age and Rates of Primary and Secondary Syphilis Among Women, 1997–2006

CS cases (in thousands)

P&S rate (per 100,000 women)
Primary Syphilis - Chancres

Photos courtesy of Joseph Engelman, MD, San Francisco City Clinic
Secondary Syphilis

Rash

Mucous Patches

Condylomata Lata

Photos courtesy of Joseph Engelman, MD, San Francisco City Clinic
Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis

Christina M. Marra,1,2 Clare L. Maxwell,1 Lauren C. Tantalo,1 Sharon K. Sohi,1 and Sheila A. Lukehart2
Departments of 1Neurology and 2Medicine, Division of Infectious Diseases, University of Washington, Seattle

- Normalization of serum RPR predicts resolution of neurosyphilis
  - 91-97% with 4-fold decline/normalization serum RPR had resolved CSF abnormalities by 13 months
  - HIV-infection lowered association but increased with HAART

Hot Off The Press

Clinical Ophthalmologic Findings and Syphilis Serology Poorly Predict Neurosyphilis

- 52 patients with ocular disease underwent an LP:
  - 35 (67%) RPR-/FTA+ and 17 (33%) RPR+/FTA+.
- Ocular pathology was comparable in each group.
- No reactive CSF VDRLs were found in either group.
- Current recommendations to perform an LP on anyone with serologic tests consistent with syphilis and ophthalmic symptoms need to be more specific

Case 1

• A 46-year-old HIV-positive homosexual man was admitted to hospital with an eight-week history of worsening left frontal headaches poorly controlled by analgesics.
• He had been HIV-positive for over 20 years and had been on a consistent antiretroviral regimen that included didanosine, abacavir and lamivudine.
• He took a two-month ‘drug holiday’ and then resumed taking his medications just prior to the onset of his symptoms.
• He reported having new sexual partners.

Case 1

• On admission to hospital, his neurological examination was normal, his CD4 T cell count was 340 cells/mm$^3$ and a computed tomography scan showed a left frontal lobe mass.

• The differential diagnosis included lymphoma, toxoplasmosis, a solitary metastasis and brain abscess.

• Antitoxoplasmosis therapy had no effect on the brain lesion.

Case 1

- Lumbar puncture was performed: CSF VDRL reactive (1:8).
- Serum rapid plasma reagin (RPR) test reactive at 1:1024, TPPA+.
- Brain biopsy showed intense lymphoproliferative infiltrates of plasma cells and T lymphocytes. B-cell infiltrates were also present.
- PCR positive for *T. pallidum*. Warthin-Starry stain demonstrated the presence of spirochetes.


Polymerase chain reaction amplification of *po1A* gene fragment (377 bp) of *Treponema pallidum* from the paraffin embedded abnormal biopsy material.
Case 1

• The patient was started on intravenous penicillin; his headaches disappeared as did his fever and rash. His RPR declined and the brain lesion resolved on subsequent neuroimaging.

• Cerebral gummas, rare manifestations of neurosyphilis, are reported sporadically. The profusion of spirochaetes in this gumma (which is unusual) was likely due to his immunosuppression.

• It is highly unusual for secondary and tertiary syphilis stages to overlap.
Neurosyphilis Treatment

- Intravenous aqueous penicillin G 18-24 MU daily x 10-14 days

- *Penicillin-allergic:*
  - **Non-Pregnant:**
    - Ceftriaxone 1-2 gm IV qD x 10 days
    - Doxycycline 100 mg PO BID x 14-21 days
  - **Pregnant:**
    - Test for hypersensitivity, desensitize, treat with penicillin

- Follow with 1-3 IM injections penicillin G benzathine 2.4 MU IM weekly

Treatment Follow-up

- Repeat CSF analysis every 6 months until normal

**Serology**

- In HIV-infected patients: 3, 6, 9, 12 and 24 months
  - 4-fold decline by 12 months consistent with cure
  - Failure of 4-fold at 12-24 months may necessitate repeat treatment

- In HIV-uninfected patients: 6 and 12 months
  - 4-fold decline by 6 months consistent with cure
  - Failure of 4-fold at 12 months may necessitate repeat treatment
Partner Treatment

- All sex partners in the prior 6 months (secondary) should be notified

- Those with recent sexual contact (≤ 90 days) should receive epidemiologic treatment

- Penicillin G benzathine (Bicillin® L-A)* 2.4 million units (MU) intramuscular (IM) once

- **Penicillin-allergic:**
  - Non-Pregnant: Doxycycline 100 mg PO BID x 14 days
  - Pregnant: Test for hypersensitivity, desensitize, treat with penicillin G benzathine 2.4 MU IM once

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**Do not substitute** Bicillin® C-R for Bicillin® L-A in the treatment of syphilis. Bicillin® C-R is NOT indicated for the treatment of syphilis.

Summary

• Syphilis is increasing in the United States
  – Highest rates in African-Americans
  – Most cases occurring in gay men and other men who have sex with men

• Treatment of neurosyphilis requires use of aqueous penicillin G

• When using penicillin G benzathine (Bicillin® LA), avoid Bicillin® C-R, not indicated for syphilis
More Information and Questions!

- SFDPH City Clinic
  www.sfcityclinic.org
  Jeff.Klausner@sfdph.org

- State of CA STD Branch
  www.std.ca.gov

- CDC STD Treatment Guidelines 2006
  www.cdc.gov/std

- www.Bicillin.net
Questions?

Ask Dr. Klausner ("Dr. K")
Thank You

Please look for your next version of the “Syphilis Today” newsletter

More information available at www.bicillin.net

Special thanks to CSI Medical Education and King Pharmaceuticals