Syphilitic Uveitis

C. Michael Samson, M.D.

Case Presentation

CC: 81 year old woman referred for corneal ulcer OD

HPI: An 81 year old woman was referred by her local ophthalmologist for treatment of a severe corneal ulcer. She had no recent history of trauma, and was not a contact lens wearer. She had previously been on topical steroids for chronic uveitis, which had been discontinued in the infected eye. She had been on fortified antibiotic drops with minimal effect for 3 days when she presented.

POH: Past ocular history is significant for a chronic, bilateral, non-granulomatous uveitis, which had been treated with PredForte bid. She had dense cataracts OU, and a history of light perception vision OD for many years. Her local ophthalmologist had deferred cataract surgery due to the fact that he had never been able to completely control her uveitis. The patient had been registered as legally blind for at least ten years.

PMH: Arthritis, adult onset

Physical Exam:

Va OD LP OS CF @ 2 ft

EOMI Pupils: could not assess APD because of synechiae ou

Corneal sensations intact OU

SLE OD +central corneal infiltrate with 50% thinning (-) satellite lesions

+band keratopathy

+anterior and posterior synechiae

+10% hypopyon

+brunescent cataract, dislocated

OS + trace cells

+posterior synechiae

+brunescent cataract

DFE OD B-scan revealed no retinal detachment, mass, or vitreous debris.

OS B-scan revealed no retinal detachment, mass, or vitreous debris.

Assessment:

1. Corneal ulcer OD with threatening perforation
2. Chronic uveitis OU
3. Mature Cataracts OU, with dislocation OD
4. Light perception vision, OD

Plan:

1. Scrape, Gram stain, cultures
2. Admit for corneal ulcer; initially broad spectrum fortified antibiotics, pending culture
3. Work up of uveitis
4. Consider cataract extraction OS when uveitis controlled

Clinical Course

The patient's Gram stained corneal scraping showed Gram-negative bacilli, and culture grew Pseudomonas. Patient's infection responded well to the appropriate fortified antibiotics, and the integrity of the globe was preserved without need of a surgical procedure.

Lab test revealed a positive RPR and FTA, which were both repeated and confirmed. The patient did not recall a history of sexually transmitted diseases or blood transfusion. The patient was treated with Penicillin G 3 million units IV q4h x 14 days (neurosyphilis regimen). The patient's uveitis resolved without need of topical steroids. The patient underwent cataract extraction OS three months later, and had an uncomplicated postoperative course with a final acuity OS of 20/30.

Discussion: Syphilitic Uveitis

ETIOLOGY

The disease was first described in detail by Nicolaus Leonicenus, an Italian physician, at the end of the 15th century, which coincided with the return of the first European explorers from the New World. Charles the VIII of France invaded Naples with a mercenary army from all over Europe, which included infected Spanish soldiers. The disease spread among the camps, and came to be known as the "French Pox" (note: this was how it was known by the Italians; the French had their own name for it: "the Neopolitan Pox"). After the wars, the soldiers returned to their home countries, and syphilis subsequently became endemic in Europe.

The name "syphilis" originated from a poem written in 1530 by the Italian poet Hiero Fracastor. In his poem, the main character, a shepherd named "Syphillus", was infected with the disease.

Little headway was made in treating syphilis until 1905, when Schaudin and Hoffman isolated the spirochete *Treponema pallidum* from skin lesions of infected patients (Fig 1). Soon to follow, it was noted that patients with syphilis created antibodies against extracts of normal mammalian tissues, specifically cardiolipin. Wasserman introduced a test to detect these antibodies in 1910.

The first effective treatment cane in 1943, with the discovery of penicillin. Finally, a big step in the control of this worldwide disease came this year, as researchers and scientists have mapped the entire genome of Treponema pallidum.

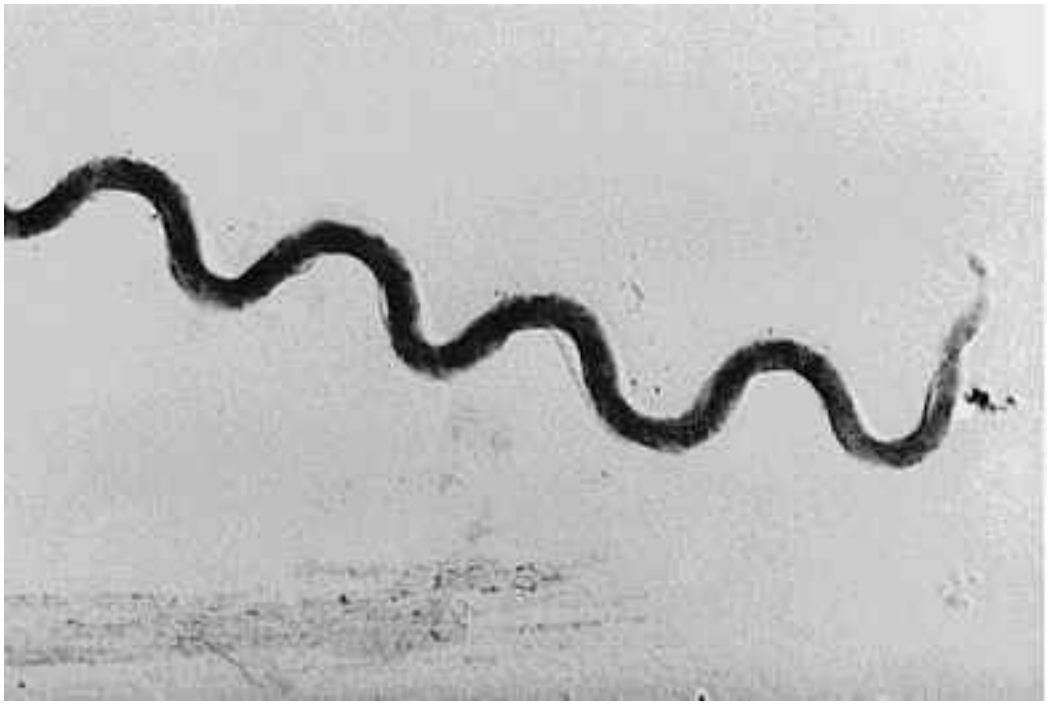

Figure 1. The spirochete *Treponema Pallidum*.

CLINICAL MANIFESTATIONS

Since syphilis had been described for 500 years before a (successful) treatment was available, much is known about its natural history. The progression in its natural history has been divided in distinct clinical stages.

The first stage, primary syphilis, is characterized by the chancre, which initiates at the inoculation site, usually in the genitalia region.

If untreated, the disease will progress to secondary syphilis, which is characterized by a generalized rash and lymphadenopathy, occurring 4 to 10 weeks after the initial manifestation of the disease. Symptoms typically include fever, malaise, headache, nausea, anorexia, and joint pains. Many other organs can be involved at this stage, including the liver, kidneys, GI tract. The eyes are affected in approximately 10% of cases.

The following period is called the latent stage, and is divided into early latent (up to one year after initial infection) and late latent (after one year). Most untreated patients will remain in this stage, but up to 30% will progress on to tertiary syphilis.

Tertiary syphilis can be defined into three major groups: 1) benign tertiary syphilis, 2) cardiovascular syphilis, 3) neurosyphilis. The characteristic lesion of benign tertiary syphilis is the gumma. Histologically, the gumma is a granuloma. They are usually found in the skin and mucous membranes, but can occur anywhere in the body, and have been found in the choroid

and iris. Cardiovascular syphilis can involve the coronary arteries or aorta. Neurosyphilis can affect the CNS via vascular pathways or direct involvement of parenchyma.

SYPHILIS FEATURES – ANTERIOR UVEITIS

Though it can occur acutely during early secondary syphilis, syphilitic uveitis will take on a chronic course if untreated. It may be bilateral: the series by Tamesis and Foster showed a slight predominance of unilateral involvement at 56%. Syphilitic uveitis is one of the few types of uveitis that will commonly present as a granulomatous inflammation, and can present with iris nodules similar in appearance to those seen in other granulomatous diseases. In Barile and Flynn's series, 2/3 of their patients with anterior uveitis was of a granulomatous nature. Syphilitic uveitis can present in conjunction with interstitial keratitis.

SYPHILIS FEATURES – POSTERIOR UVEITIS

Syphilis can affect the posterior segment. In the series done here, Tamesis and Foster found of the patients with syphilitic uveitis, 18% had posterior uveitis, and 47% had panuveitis. Barile and Flynn series showed 9% posterior and 27% panuveitis. The posterior involvement can take on many different forms, such as vasculitis, macular edema, stellate maculopathy, pseudo-RP, and neuroretinitis. Other presentations not listed here include diffuse chorioretinitis, uveal effusion, CRVO, SNVM formation, and retinal necrosis. Gass in 1990 coined the term "syphilitic posterior placoid chorioretinitis" where he described six patients with secondary syphilis who showed one or more macular or juxtapapillary placoid lesions at the level of the RPE.

DIAGNOSIS

Diagnosis is by clinical history, physical exam, and laboratory tests.

T. Pallidum cannot be cultured continuously, so diagnostic methods rely on serologic tests.

Infection with *T. Pallidum* stimulates nonspecific antibodies against cardiolipin. The Veneral Disease Research Laboratory test and the Rapid Plasma Reagin (RPR) test quantitate the amount of anticardiolipin antibody present in serum, giving a result as reactive, weakly reactive, borderline, and non-reactive. The sensitivity and specificity depend on the stage of syphilis and status of treatment.

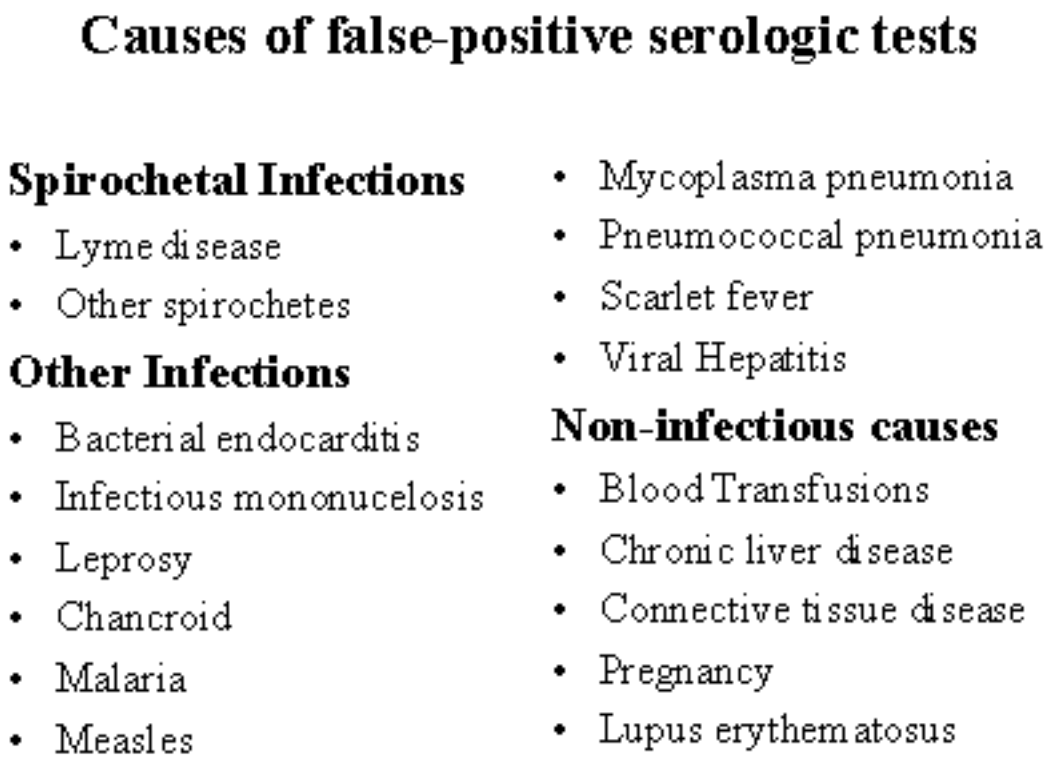

Figure 2. Causes of false-positives RPR / VDRL.

There are many causes of false-positive serologic tests for syphilis (see Fig 2), in particular, other spirochetal diseases and certain connective tissue diseases. Because of this, we have more specific laboratory tests for syphilis. There is TPI, or T.Pallidum immobilization test, which is almost completely specific for syphilis, but very expensive and difficult to perform. FTA-ABS tests for antibodies specifically against T Pallidum. FTA is not 100% specific, and can be falsely positive in entities like SLE, biliary cirrhosis, and rheumatoid arthritis. Immediate diagnosis can be obtained by direct visualization of the organisms by Darkfield Microscopy.

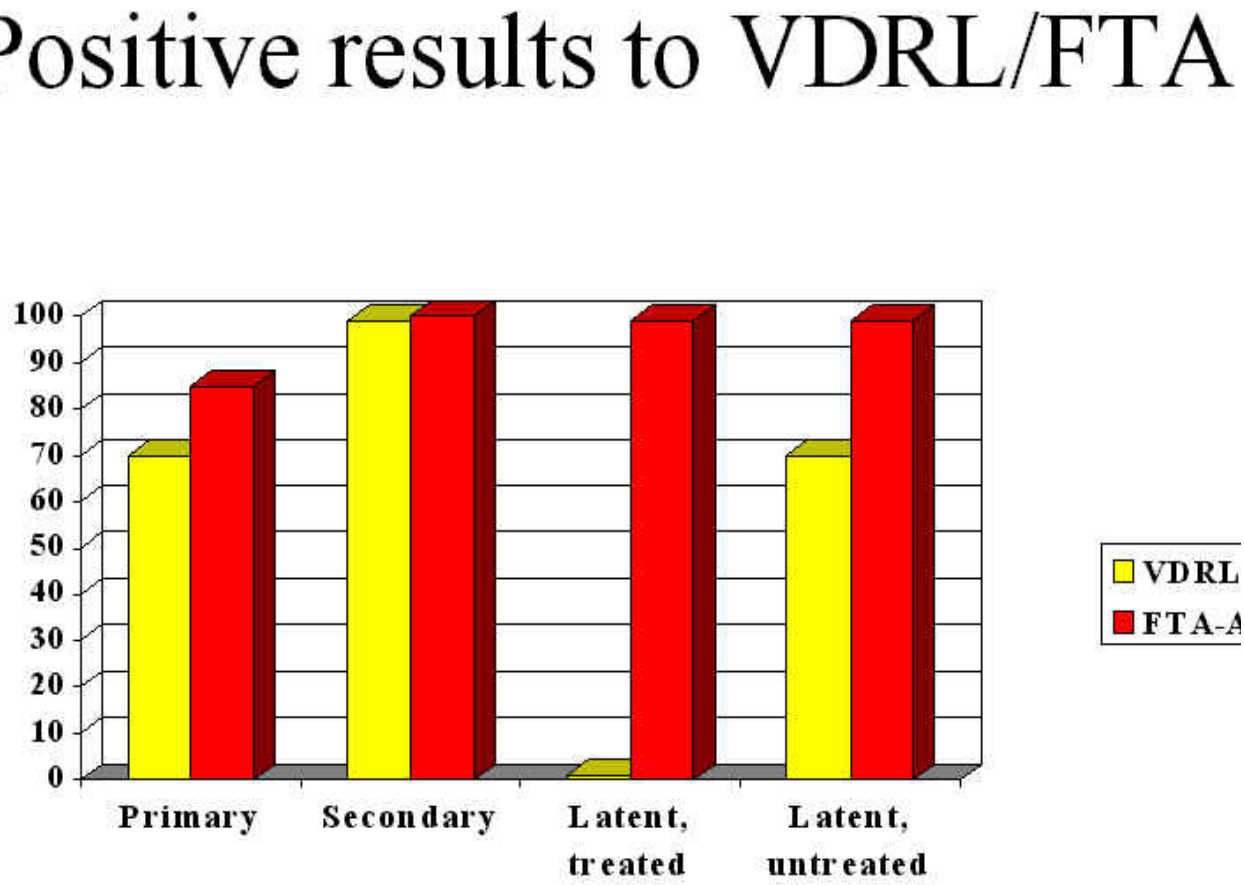

Figure 3. Percentage of positive results of VDRL and FTA in different stages of syphilis.

SENSITIVITY

The chart in **Figure 3** helps illustrate why one must request FTA-ABS. As you can see, the VDRL and FTA are comparable in primary and secondary disease, the sensitivity increasing from 70% and 85% to 99% and 100%, as the anticardiolipin antibodies increase. However, from an ophthalmologic point of view, most patients will be suspected of having untreated latent syphilis, and VDRL will miss 30% of these patients, while an FTA will detect almost all of them.

TREATMENT

Uveitic syphilis should be considered a form of neurosyphilis, and treatment should be accordingly. The recommendation of the CDC for late latent syphilis is Penicillin injections weekly for 3 weeks; these recommendations are based on empiric clinical judgement, and not on syphilis treatment trials. Also, there are multiple reports in the literature of treatment failures with penicillin. To make a point, in Barile and Flynn's paper, 34% of their patients with syphilitic uveitis had already undergone treatment, though they do state that the previous treatment was poorly documented, poorly recalled, and appeared incomplete in many cases.

WHAT'S NEW

The complete genome of *Treponema pallidum* has been determined: 1.1 million base pairs, containing 1041 open reading frames. To know the impact of this, one should remember that *T. Pallidum* cannot be continuously cultured in the lab, and this fact has frustrated scientists ability to study the pathogenic mechanisms of the organism, as well as develop a vaccine. Now this will change, as study of *T. Pallidum*'s open reading frames and their protein products will help scientists uncover many of the questions we still have. They will help in developing a method of culture, studying the virulence factors of the organism, develop perhaps more specific and sensitive diagnostic tests, and possibly develop a vaccine. This landmark paper was published in the July 17 issue of Science magazine.

References

1. Barile, Flynn, "Syphilis Exposure in Patients with Uveitis", *Ophthalmology* 1997; 104:1605-1609
2. Cumston, C.G., "The History of Medicine", Dorset Press, 1987.
3. Fraser, C et al, "Complete Genome Sequence of Treponema pallidum, the Syphilis Spirochete", *Science* July 1998; 281:375-388
4. Margo, C, Hamed, L, "Ocular Syphilis", *Surv Ophtalmology* 1992; 37(3):203-220
5. Nussenblat R, Whitcup S, Palestine A, "Uveitis: Fundamentals and Clinical Practice", Second edition, Mosby-Year Book, 1996.
6. Tamesis, Foster, "Ocular Syphilis" *Ophthalmology* 1990; 97:1281-1287

Review Questions for Syphilitic Uveitis

C. Michael Samson

1. The causative organism for Syphilis is:

a. *Treponema carateum*

b. *Treponema pallidum*

c. *Borellia burgdorferi*

d. *Leptospira interrogans*

2. The following terms are matched correctly EXCEPT:

a. Primary syphilis – chancre

b. Secondary syphilis – lymphadenopathy

c. Secondary syphilis - neurosyphilis

d. Latent syphilis – uveitis

e. Tertiary syphilis – Tabes Dorsalis

3. The following statements about syphilitic anterior uveitis are true EXCEPT:

a. May present as unilateral or bilateral

b. Rarely presents as granulomatous uveitis

c. Usually occurs in latent syphilis, but may occur in secondary syphilis

d. Can present in conjunction with interstitial keratitis

4. Syphilitic posterior uveitis manifestations include:

a. Pseudo-retinitis pigmentosa

b. Neuroretinitis

c. Retinal vasculitis

d. All of the above are correct

e. Only b and c are correct

5. Diagnosis of syphilitic uveitis is usually made by

a. Serologic tests

b. An iritis associated with a chancre

c. Classic appearance on fluorescein

d. Culture

6. Known causes of false positive RPR include all of the following EXCEPT:

a. Yaws

b. Advanced age

c. HIV

d. Chronic liver disease

e. Wegener's granulomatosis

7. FTA testing should be ordered in patients with uveitis suspected to be secondary to syphilis because:

a. One can follow the FTA to assess success of treatment

b. FTA is more specific for spirochetes that invade the eye

c. Most uveitis occurs in latent syphilis, during which FTA is much more sensitive than RPR

d. FTA is not associated with false positives

8. The definitive treatment for syphilitic uveitis is

a. Predforte drops for acute control, then topical NSAIDS chronically

b. Augmentin 500 mg PO BID x 3 weeks

c. Procaine penicillin 50,000 units/kg/day IM x 10 days

d. Penicillin G 2.0 – 4.0 million units IV q4h x 10 days

9. The determination of the complete genome of the causative organism of syphiliswill benefit its management by:

a. development of a culture method

b. study of virulence factors

c. development of more specific and sensitive tests

d. development of a vaccine

e. all of the above

Answers:

1. B
2. C
3. B
4. D
5. A
6. E
7. C
8. D
9. E