Serologic Testing for the Diagnosis of Syphilis among Patients with Non-specific Uveitis

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INTRODUCTION

The incidence of syphilis has risen in the United States since 2000, especially among HIV-infected individuals. Other groups at high risk include men who have sex with men; individuals with multiple sexual partners; those with histories of incarceration; and commercial sex workers. Since 2015, a large number of individuals with ocular syphilis have been reported; in many cases, the diagnosis was not considered initially, emphasizing the need for diagnostic testing of patients with non-specific intraocular inflammation.

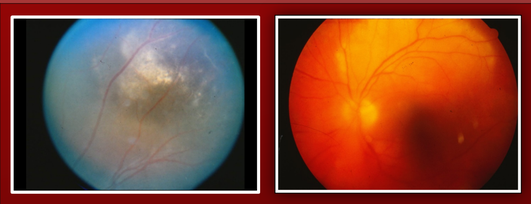

Figure 1 (left). Syphilitic retinitis in a man with AIDS.
Figure 2 (right). Subretinal placoid chorioretinitis in a man with AIDS.

There are two approaches to testing: (1) traditional screening with a non-treponemal test (RPR, VDRL), followed by a treponemal test for confirmation, if the screening test is reactive; and (2) reverse-sequence screening with a treponemal test first. The United States Preventative Services Task Force has published guidelines for screening high-risk groups, using the traditional approach.[1]

Because most patients with non-specific intraocular inflammation are at low-risk for syphilis, uveitis specialists generally advocate reverse-sequence screening, because ocular involvement often occurs in later stages of the disease, when non-treponemal tests become non-reactive. For example, Moradi and associates found that 5 (31%) of 16 HIV-negative patients with ocular syphilis had non-reactive RPR tests (100% reactive FTA-Abs tests);[2] however, there are no data regarding the frequency of this combination of test results among unselected patients with uveitis.

METHODS

We reviewed the medical records of all new patients with uveitis seen by 8 uveitis specialists at one tertiary referral center in Baltimore, MD during the period 2013-2017. We collected the following information for each patient: age; non-treponemal (RPR, VDRL) and treponemal (FTA-Abs, TP-PA) test results; HIV infection status; category of uveitis; whether or not a final diagnosis of syphilis was made, history of prior syphilis (and prior treatment, if applicable).

A diagnosis of syphilitic uveitis was made if the patient met one of the following criteria:

- A reactive treponemal test that was confirmed with a reactive non-treponemal test or second treponemal test and no other identifiable cause for uveitis.
- A non-ocular manifestation of syphilis.
- A remote history of syphilis, without confirmation of adequate treatment, and a reactive non-treponemal test.

We report the prevalence of syphilitic uveitis among patients with uveitis, as well as the positive predictive value (PPV) and negative predictive value (NPV) for non-treponemal and treponemal tests.

RESULTS

Medical records were reviewed for 442 patients, 310 of whom had at least one test for syphilis. Non-treponemal tests were performed on 90 patients and treponemal tests were performed on 272 patients. Both types of tests were performed on 52 patients (results available for 50 patients). Among 310 patients tested, 14 (4.5%) were diagnosed with syphilitic uveitis; they accounted for 3.2% of all uveitis cases.

Table 1. Diagnostic test results for 50 patients with non-specific uveitis who had both non-treponemal and treponemal tests.

Diagnostic Test		Number of Cases	Number with Syphilitic Uveitis
Non-Treponemal	Treponemal		
Reactive	Reactive	13	12
Reactive	Non-reactive	0	--
Non-reactive	Reactive	4	2
Non-reactive	Non-reactive	33	0

Among the 50 patients with results for both types of tests, both were reactive for 13 patients, 12 of whom had active syphilis; one patient had a persistently reactive RPR at low-titer, following adequate treatment for neurosyphilis and was believed not to have active disease (Table 1). Four of 50 (8.0%) had non-reactive RPR and reactive FTA-Abs test results; 2 had active syphilitic uveitis, while the other two had histories of previous, adequately treated syphilis with recent onset of unrelated anterior uveitis (Table 2).

For non-treponemal tests, the positive predictive value (PPV) for active syphilitic uveitis was 92.3% (12/13) and the negative predictive value (NPV) was 97.4% (75/77). For treponemal tests, the PPV for active syphilitic uveitis was 82.4% (14/17), and the NPV was 100% (253/253).

Table 2. Characteristics of 4 patients with non-reactive RPR / reactive FTA-Abs test results.

Case	Age (Years)	Prior Diagnosis of Syphilis	Current Active Syphilis	HIV-Infected	Ocular Findings	Non-ocular Findings
1	54	No	Yes	No	CAU	None
2	46	No	Yes	Unknown	Retinal vasculitis	None
3	65	Yes	No	No	AU, recent onset*	None
4	55	Yes	No	Yes	AU, recent onset*	None

AU = anterior uveitis, CAU = chronic anterior uveitis.
*There was no evidence of active syphilis in either case, and both were treated appropriately for neurosyphilis; uveitis was believed not to be related to syphilis, but the causes were not determined.

DISCUSSION

Despite the low prevalence of syphilitic uveitis, continued testing of all patients with non-specific intraocular inflammation is warranted for the following reasons: treatment of syphilitic uveitis differs from most other forms of uveitis; there is substantial public health risk and potential morbidity with unrecognized cases; there are no pathognomonic signs of syphilitic uveitis; and laboratory tests can establish the presence of infection.

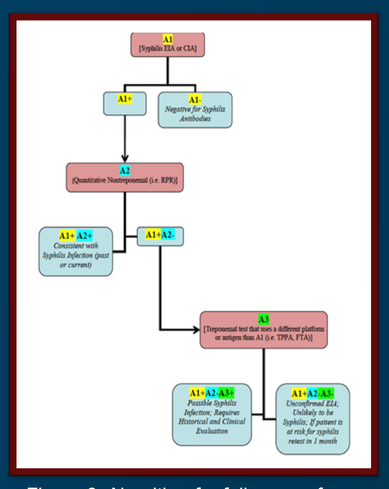

Figure 3. Algorithm for follow-up of a reactive treponemal test in reverse-sequence screening for syphilis.[3]

Non-reactive treponemal tests were uncommon in our population (4%); however, we continue to advocate reverse-sequence testing, to avoid missing cases of syphilitic uveitis in patients with late-stage disease.

Following treatment of syphilis, treponemal tests remain active for life, while non-treponemal tests may revert to non-reactivity; thus, serologic testing will also identify a remote history of treated infection. It is therefore critical to perform follow-up testing of reactive treponemal tests when used in reverse-sequence screening, as outlined in Figure 3.

This study is limited by its retrospective nature, lack of standardized testing procedures, and small number of cases with results for both types of tests. Diagnoses of syphilitic uveitis were made by exclusion of other causes. Patient were seen at an urban tertiary referral center and thus, results may not be generalizable to all patients with ocular syphilis.

CONCLUSIONS

- Our study confirms the low prevalence of ocular syphilis among patients with non-specific intraocular inflammation, even in a tertiary referral practice. Patients with uveitis in general should be considered a low-risk population for syphilis.
- Despite the low prevalence of ocular syphilis, routine diagnostic testing for syphilis is appropriate.
- Discordant results on serologic testing are uncommon, but do occur.
- Our results support the use of reverse-sequence testing, because of the possible occurrence of nonreactive non-treponemal tests, despite active disease.
- Because discordant results may also reflect remote, adequately treated disease (in patients with uveitis due to other causes), follow-up with non-treponemal, and possibly alternate treponemal tests, must be performed to confirm a diagnosis of active disease.

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