

Are serological tests of value in diagnosing and monitoring response to treatment of syphilis in patients infected with human immunodeficiency virus?

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SUMMARY To assess the value of serological tests in diagnosing and monitoring the response to treatment of syphilis in patients infected with the human immunodeficiency virus (HIV), case notes of eight homosexual men with a history of treated syphilis, positive reactions to serological tests for syphilis, and documented subsequent conversion to HIV seropositivity were studied. No change was noted in serological markers of syphilis after HIV infection. The case notes of one man with primary syphilis, four men with secondary syphilis, and three men with latent syphilis, of whom all were HIV seropositive, were also studied. In seven of these patients the serological responses to infection and after treatment were consistent with the experience of syphilis in HIV seronegative patients. In one man treated for secondary syphilis, and confirmed as HIV seropositive eight months after treatment, the rapid plasma reagin (RPR) test result continued to be positive at a high titre for up to 20 months after treatment.

Well documented deficiencies in the immune system may occur after infection with the human immunodeficiency virus (HIV). Lymphopenia is characteristic and largely due to a reduction in the total number of T4 lymphocytes, but qualitative as well as quantitative abnormalities have also been shown.¹ B lymphocytes are present in normal numbers, but show increased spontaneous immunoglobulin production and are refractory, both *in vitro* and *in vivo*, to further stimulation with B cell mitogens and neoantigens.² The resultant immunological deficiencies predispose to the infections seen in the acquired immune deficiency syndrome (AIDS), and may mask the various clinical features on which diagnosis of disease depends.

The host response to infection with *Treponema pallidum* is complicated and affects many components of the immune system.³ In particular, B cell activation may be inferred from the type of antibodies present in the serum of infected people. The diagnosis of syphilis

relies to a large extent on showing the production of antibody, and these responses could theoretically be altered as a result of immunodeficiency associated with HIV infection.

To investigate this theory, we decided to examine the case records of two groups of patients with syphilis. The first group, group A, consisted of homosexual men with a history of treated syphilis, positive reactions to serological tests for syphilis, and documented subsequent conversion to HIV seropositivity. Could polyclonal B cell activation lead to changes in serological markers of syphilis after infection with HIV?

The second group, group B, consisted of homosexual or bisexual men diagnosed and treated for syphilis, all of whom were found to be HIV seropositive at the time of diagnosis or during serological follow up after conventional treatment. Could serological responses to infection with *T pallidum*, and after treatment, be affected by concurrent HIV infection?

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Patients and methods

Patients in group A were eight men from a cohort of homosexual men who were at risk of HIV infection and had been followed up prospectively at this clinic since 1982.⁴

Patients in group B consisted of eight homosexual

or bisexual men diagnosed and treated for syphilis from September 1985 to December 1986 at this clinic. Treatment of all patients consisted of two intramuscular injections of benzathine penicillin 2.4 MIU given one week apart.

SEROLOGICAL TESTS FOR SYPHILIS

All serum samples were tested in the diagnostic microbiology laboratory of this hospital. Routine serological tests included the rapid plasma reagin (RPR) test, the *T pallidum* haemagglutination assay (TPHA), and the fluorescent treponemal antibody absorption (FTA-ABS) test.

DIAGNOSIS OF HIV INFECTION

Since September 1985 all serum samples have been tested using a competitive enzyme linked immunosorbent assay (ELISA) technique (Wellcome Diagnostic Laboratories). Samples giving positive results were repeat tested for confirmation using an alternative ELISA technique (Abbot Laboratories). Before September 1985 serum samples were tested using a fixed cell membrane immunofluorescence technique as described previously.⁵

Results

The eight men in group A (cases 1–8) were of west European origin. HIV infection was classified in all cases, according to the guidelines of the Centers for Disease Control (CDC),⁶ at the time of the last available results of serological tests for syphilis for all patients (table 1).

The TPHA gave positive results in all cases. One or more positive RPR test results were available for all patients at a time when they were documented as being HIV seronegative, and these results preceded conversion to HIV seropositivity by one to 24 (median 10) months. Five patients had RPR tests at the time of documented seroconversion and there was no difference when compared with the results of RPR tests preceding seroconversion. Four patients had RPR tests on one or more occasion one to 15 (median 4) months after seroconversion. Table 2 shows that none of them experienced a rise in RPR titre.

Of the eight men in group B (cases 9–16), seven were of west European and one of Australian origin. HIV infection was classified in all cases, according to CDC guidelines, at the time of diagnosis of syphilis or of HIV seropositivity if later (table 1). Individual case reports follow. In all cases, either the TPHA or both the TPHA and the FTA-ABS test gave positive results at the time that syphilis was diagnosed.

CASE 9

A man aged 23 presented with an indurated penile

ulcer. Dark ground examination for *T pallidum* gave negative results on two occasions. Initially negative, the RPR test result became positive 16 days later at a titre of 1/16, and the patient was diagnosed as being HIV seropositive. Primary syphilis was diagnosed and treated. At 36 days after treatment the RPR test result was positive at a titre of 1/1.

CASE 10

A man aged 33 presented with the RPR test giving a positive result at a titre of 1/512. He defaulted, but returned two months later with a generalised macular and maculopapular skin rash, when the RPR test result was positive at a titre of 1/256. Secondary syphilis was diagnosed and treated. RPR tests 234 and 291 days after treatment gave positive results at titres of 1/32 and 1/8, respectively. At the latter visit, he was diagnosed as being HIV seropositive.

CASE 11

A man aged 40, who had a history of treated syphilis in 1976 and 1980, presented in 1985 with a perianal ulcer and a rash affecting the skin of the arms and right hand. Dark ground examination showed *T pallidum*, and the RPR test result was positive at a titre of 1/512. Secondary syphilis was diagnosed and treated. At 22 and 84 days after treatment, the RPR test result was positive at titres of 1/1024 and 1/64, respectively. At 236 days after treatment the RPR test result was positive at a titre of 1/16 and HIV seropositivity was diagnosed. In the following months, the RPR test result remained positive at titres ranging from 1/16 to 1/64. He was treated again 19 months after initial treatment, but failed to return for further follow up.

CASE 12

A man aged 29 presented giving a history of nocturnal fever and a skin rash affecting both arms. The RPR

Table 1 Centers for Disease Control classification of HIV infection in two groups of homosexual men

| Case | Classification | Case | Classification |
|----------------|---|------|----------------|
| <i>Group A</i> | | | |
| 1 | Group II | 9 | Group III |
| 2 | Group II | 10 | Group III |
| 3 | Group III | 11 | Group II |
| 4 | Group III | 12 | Group III |
| 5 | Group II | 13 | Group II |
| 6 | Group II | 14 | Group II |
| 7 | Group IV C-2 (oral candidiasis) | 15 | Group II |
| 8 | Group IV C-1 (oesophageal candidiasis) | 16 | Group III |

Group A = men with histories of treated syphilis, positive results to serological tests for syphilis, and documented subsequent seroconversion to HIV positivity.

Group B = men diagnosed as having syphilis who were HIV seropositive at diagnosis or during follow up after treatment for their syphilis.

Value of serological tests in diagnosing and monitoring response to treatment of syphilis in patients with HIV 221

Table 2 Rapid plasma reagin test results* before and after documented conversion to HIV seropositivity in group A men†

| Case | Months preceding seroconversion | | | | | | | | | | | | Months after seroconversion | | | | | | | | | | | | | | | | | |
|------|---------------------------------|----|-----|-----|----|----|----|----|----|----|----|----|-----------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|----|
| | 24 | 23 | 22 | 21 | 20 | 19 | 18 | 17 | 16 | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 14 | 15 |
| 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | | | Neg | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | | | | Neg | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | 1/4 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

*Titres given for positive results.
†For definition of group A men, see footnote to table 1.

test result was positive at a titre of 1/32, and he was HIV seropositive. Secondary syphilis was diagnosed, but he failed to return for treatment. Attempts to trace him were unsuccessful.

case 13

A man aged 26, known to be HIV seropositive, presented giving a history of sweating at night. Serial RPR tests showed positive results at titres of 1/128 and 1/64. Secondary syphilis was diagnosed and treated. At 49 days after treatment the RPR test result was positive at a titre of 1/2. At 147 and 252 days after treatment the RPR test results were negative.

CASE 14

A man aged 22 presented requesting HIV antibody testing. He was seropositive, and serial RPR test results were positive at titres of 1/4 and 1/1. Latent syphilis was diagnosed and treated. At 50 days after treatment the RPR test result was positive at a titre of 1/1.

CASE 15

A man aged 35 presented requesting HIV antibody testing. He was seropositive, and serial RPR test results were positive at titres of 1/16 and 1/8. Latent syphilis was diagnosed and treated. At 40 days after treatment the RPR test result was positive at a titre of 1/4, and at 155 days it was negative.

CASE 16

A man aged 26, who had a history of treated syphilis in 1980, presented in 1986 with a perianal fissure. Dark ground examination for *T pallidum* was negative, but serial RPR test results were positive at titres of 1/64 and 1/32. Early latent syphilis was diagnosed and treated. At 118 days after treatment the RPR test result was positive at a titre of 1/1.

Discussion

Serological testing remains the most important tech-

nique available for diagnosing syphilis, but the value of these tests in patients infected with HIV needs to be assessed in the light of the recognised effects of this virus on B cell function.² Polyclonal B cell activation leads to increased production of antibodies directed against previously encountered antigens. In patients with a history of treated syphilis it is possible that, after HIV infection, changes might be observed in syphilis serological test results, notably the quantitative non-treponemal tests, which may lead to diagnostic confusion. The study of patients in group A, however, provided no evidence that this occurs.

A consequence of the inability of B cells in HIV infected patients to respond to neoantigens, is the unreliability of serological diagnosis of infections. This has been reported for both toxoplasmosis⁷ and cytomegalovirus infection.⁸ In our eight patients with syphilis and HIV infection (group B), serological responses to infection were no different from those observed in HIV seronegative people. In six cases, the serological responses after treatment were satisfac-

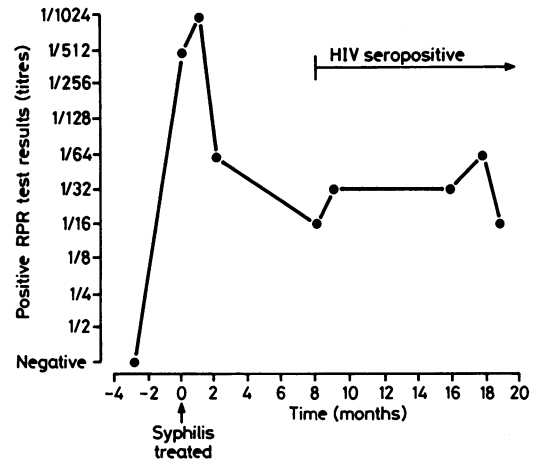


Figure Rapid plasma reagin (RPR) test results in one man (case 11) before and after treatment for secondary syphilis and in relation to his becoming HIV positive.

tory, but in one patient (case 11) who was treated for secondary syphilis the RPR test result remained positive at a high titre after HIV seropositivity had been diagnosed (fig).

After adequate treatment of primary and secondary syphilis, the serum titre of the non-treponemal test may be expected to fall about fourfold by three months and eightfold by six months,⁹ and to be negative by 12 months (in the case of primary syphilis) or 24 months (in the case of secondary syphilis).¹⁰ The serological test results for one man (case 11) showed a satisfactory initial fall after treatment, but his persistently high RPR titres after conversion to HIV seropositivity prompts consideration of several possible explanations. Treatment failure was unlikely, as the prescribed regimen of benzathine penicillin is very effective in early syphilis. Lumbar puncture would have been advisable, however, to exclude asymptomatic neurosyphilis, which may fail to respond to treatment.¹¹ At least theoretically, this may be more common in immunocompromised people.¹² Although no new symptoms or signs of syphilis were reported in our patient, he may have been reinfected by documented new sexual contacts, or alternatively some event such as immunisation, which is associated with biological false positive non-treponemal test results, may have occurred. Either of these events could account for the observed serological response and cannot be excluded by retrospective analysis. The serological responses after treating patients who have previously had syphilis are sometimes atypical,⁹ but the persistently high titres in this patient could have been secondary to HIV infection and its effect on B cell function.

The recognition of functional B cell abnormalities by Lane *et al* resulted from studies of homosexual men with AIDS.² In this study, most patients were classified as CDC group II or group III, and only two (cases 7 and 8) were classified as group IV. This study therefore documents the serological responses of a group of patients who were predominantly in the early stages of the range of HIV infection. Though it is reassuring that serological responses to infection with *T pallidum*,

and after treatment, appear to be preserved in HIV infected people, it is by no means clear that this will be the case in patients with more advanced disease and more profound immunodeficiency. Indeed, Hicks *et al* have recently reported a case of seronegative secondary syphilis in a patient infected with HIV and with Kaposi's sarcoma.¹³

References

- 1 Pinching AJ. *The immunology of AIDS and HIV infection*. London: WB Saunders, 1986:645-60. (Clinics in Immunology and Allergy Vol 6, No 3.)
- 2 Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;309:453-8.
- 3 Musher DM. Biology of *Treponema pallidum*. In: Holmes KK, Mårdh P-A, Sparling PF, Wiesner PJ, eds. *Sexually transmitted diseases*. New York: McGraw-Hill 1984:291-6.
- 4 Weber JN, Wadsworth J, Rogers LA, *et al*. Three year prospective study of HTLV 111/LAV infection in homosexual men. *Lancet* 1986;i:1179-82.
- 5 Pinching AJ, Weber JN, Rogers LA, Berrie EL, Jeffries DJ, Harris JRW. Longitudinal immunological studies on a cohort of initially symptom free homosexual men in London with respect to HTLV 111 serology. *Adv Exp Med Biol* 1985;187: 67-72.
- 6 Centers for Disease Control. Classification system for human T-lymphotropic virus type III/lymphadenopathy associated virus infections. *MMWR* 1986;35:334-9.
- 7 Luft BJ, Conley F, Remington JS, *et al*. Outbreak of central nervous system toxoplasmosis in Western Europe and North America. *Lancet* 1983;i:781-3.
- 8 Dylewski J, Chou S, Merigan TC. Absence of detectable IgM antibody during cytomegalovirus disease in patients with AIDS. *N Engl J Med* 1983;309:493.
- 9 Brown ST, Zaidi A, Larsen SA, Reynolds GH. Serological response to syphilis treatment. A new analysis of old data. *JAMA* 1985;253:1296-9.
- 10 Fiumara NJ. Treatment of primary and secondary syphilis: serological response. *JAMA* 1980;243:2500-2.
- 11 Markovitz DM, Beutner KR, Maggio RP, Reichman RS. Failure of recommended treatment for secondary syphilis. *JAMA* 1986;255:1767-8.
- 12 Tramont EC. Syphilis in the AIDS era. *N Engl J Med* 1987;316:1600-1.
- 13 Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. *Ann Intern Med* 1987;107:492-5.