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SHORT COMMUNICATION

Syphilis Diagnosis: Three Cases with Increasing Treponemal Test Result after Therapy

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Serology is a main tool for syphilis diagnostic work (1–3). According to a recent survey performed by the U.S. Centers for Disease Control and Prevention (CDC) 56% of infectious disease specialists responded that they send a rapid plasma reagin (RPR) test to the laboratory and treat presumptively for syphilis (if result is negative 18% repeat the RPR testing before treating the patient, and 17% treat only if RPR is positive) (4). However, a clearly positive reaction may be missing at the first visit of patients with active syphilis (5). Non-treponemal test (e.g. RPR and Venereal Disease Research Laboratory (VDRL)) reactivity is known to decrease in response to therapy, in contrast to the typically life-long persistence of treponemal test positivity. In consequence, we reasoned that it might be possible to increase the sensitivity of syphilis screening by using a treponemal test, because it has a potential for titre rise during antibiotic treatment, in contrast with the standard choice of RPR or VDRL. In this study, we present the syphilis serodiagnostic history of 3 patients where therapy was given at an early disease stage, with the aim to document the influence of antibiotics on titre development.

MATERIALS AND METHODS

The analysed patient samples were taken as part of the diagnostic clinical work, and there were no samples taken exclusively to serve for the purpose of this study. The 3 patients are men, 30–32 years of age and they were included in this study due to an exceptionally early stage of infection. Case 1 was HIV negative, presenting with ulcus penis; no sample for PCR was taken. Case 2 was diagnosed with HIV one year earlier, and was found to be syphilis serology negative 6 months earlier, with the current testing done as part of routine screening in the absence of signs of syphilis. Case 3 was HIV negative, presenting with ulcus penis, with a positive PCR reaction of an ulcus sample. All serological testing was performed in our fully accredited university hospital laboratory, participating in the UKNEQAS and the Swedish Equalis quality assessment schemes. The chemiluminescence Syphilis-TP Architect screening kit (Abbott, Abbott Park, IL, USA) was used, based on microparticles coated with treponemal antigens; a value over 1.0 is considered to be reactive (6). The non-treponemal methods are the VDRL microscopic flocculation test, performed with undiluted serum and graded 0–4 where 4 denotes a very strong reaction (an 8-fold diluted serum is also analysed on VDRL-negative sera, in order to exclude a prozone phenomenon) (antigen from Cenogenic, Morganville, NJ, USA), and the Wasserman complement fixation reaction (WR) performed with sera diluted 7.5–480 times; the 7.5 titre denoting a weak and 480 a very strong reaction (antigen from Maltaner, TCS Biosciences, Botolph Claydon, UK). A specific treponemal antigen sandwich ELISA was also used (the Captia Syphilis-Enzywell Treponema IgG and IgM, respectively, EIA from Diesse, Monteriggioni, Italy); the IgG method uses antigen-coated wells and IgM is determined by capture technique; a value over 1.0 is considered to be reactive (7). Particle agglutination was done at serum dilution 80 with no quantitation of the result (TPPA, Fujirebio, Tokyo, Japan).

RESULTS

Case 1 was tested twice, at 6 days before and 112 days after treatment start (Fig. 1, upper panel). The treponemal screening value is rising from 4 to a highly reactive value of 14, while the non-treponemal VDRL titre decreases from a weak 1 to negativity. The second non-treponemal (WR) test was negative in both samples. Treponemal IgG (EIA method) (Fig. 1, lower panel) was negative in the first sample, rising to a positive reaction after treatment, and there was no detectable IgM in any of the samples. Case 2 was tested 28 days before and 76 days after treatment start. The treponemal screening test starts out at a moderately positive value

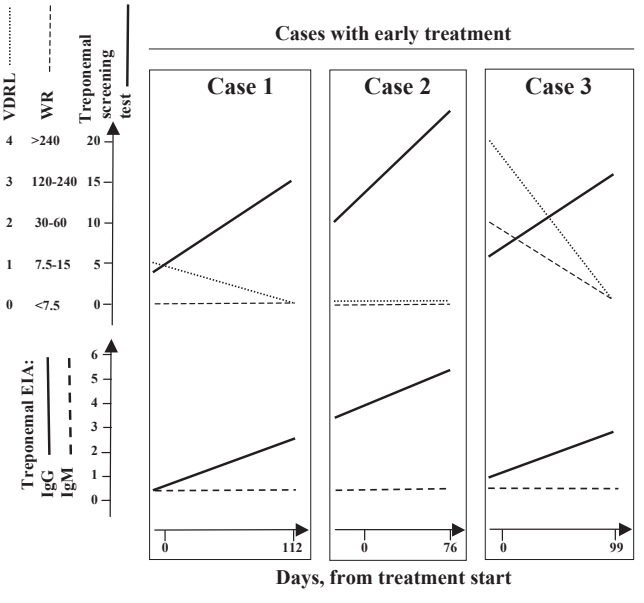

Fig. 1. Syphilis serotesting results for 3 patients where treatment was initiated at an early disease stage. A treponemal screening method and the two nontreponemal Venereal Disease Research Laboratory (VDRL) and Wasserman complement fixation reaction (WR) tests (upper panels), as well as an enzyme immunoassay (EIA) measuring treponemal IgG and IgM (lower panels) were used. Number of days from antibiotic treatment start is indicated (penicillin for cases 1–2 and doxycycline for case 3).

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of 8, rising to 22 after treatment is given (Fig. 1, upper panel). In contrast, the non-treponemal VDRL and WR were non-reactive in both samples. The treponemal EIA method showed a rise in IgG from 3.6 to 5.5, with no detectable IgM (Fig. 1, lower panel). Case 3 was tested 8 days before and 99 days after treatment was initiated. The treponemal screening test starts out at a weakly positive reaction (result is 5), increasing to 15 (Fig. 1, upper panel). VDRL is highly reactive (grade 4) and WR is moderately positive (titre 60) in the first sample, both to become negative at 99 days. With the treponemal EIA method (Fig. 1, lower panel) IgG increased from a negative 0.5 to a weak positivity of 3.0 at day 99, and there was no development of IgM. All samples, from all three cases, showed a positive TPPA result.

DISCUSSION

It is generally assumed that administration of penicillin will promptly abort any further development of treponemal antibodies, although, to the best of our knowledge, this has not been documented in the literature. We report 3 cases with a clear titre rise in specific treponemal tests occurring after antibiotic treatment had been initiated, whereas, as expected, there was no development of reactivity in non-treponemal assays. The lack of IgM development supports the view that also this parameter is sensitive to antibiotics. Our findings suggest that IgG-based treponemal tests are not influenced by antibiotic usage. Therefore, a screening algorithm based on a treponemal test, being in line with the recommendation by the European guidelines for management of syphilis, would provide serologic evidence of active syphilis in patients where treatment has been started already before a definite syphilis diagnosis is obtained (8). There are at least two clinical situations where a treponemal screening test provides increased sensitivity. Firstly, when a negative screen is observed in a patient where treatment has already been started, another sample should be taken because it may show seroconversion in a specific test. Secondly, when an antibiotic has been consumed for any reason unrelated to syphilis during the weeks preceding the date of syphilis screening. Most antibiotics are active against *T. pallidum* and can be suspected to cause a false negative non-treponemal screening result. According to the already referred to CDC survey (4), 35% of infectious disease consultants do not initiate treatment unless there is a positive RPR; arguably, in some such screening-negative cases, a specific treponemal test would have provided a positive report. A complete lack of non-treponemal test reactivity, as in case 2, may make staging of the disease and antibiotic dosage challenging; however, as in case 2, a rise in treponemal test result can then provide valuable information. In summary, our 3 cases indicate that the sensitivity of syphilis screening might be enhanced by using a specific test instead of a non-treponemal reagin method. In order for our findings to be conclusive, of course, they need to be reproduced by additional laboratories and with a larger patient material.

The authors declare no conflict of interest.

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