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The Prozone Phenomenon in Secondary Syphilis

SHOJI TANIGUCHI[1], KAZUHISA OSATO[2] and TOSHIO HAMADA[1]

[1]*Department of Dermatology, Osaka City University Medical School, and* [2]*The Osaka Prefectural Bandai Clinic for STD, Osaka, Japan*

We describe a 37-year-old woman with secondary syphilis, in whom the prozone phenomenon (false-negative test in undiluted specimens) occurred. The patient had been maintained on cyclosporine and prednisolone after renal transplantation. B-cell dysfunction induced by continuous immunosuppression may lead to higher non-treponemal serological titers. Non-treponemal testing should be repeated using serum dilutions to prevent missing the diagnosis of syphilis. ***Key words: venereal disease research laboratories test; cyclosporine.***

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S. Taniguchi, Department of Dermatology, Osaka City University Medical School, 1–5–7, Asahimachi, Abeno-ku, Osaka 545, Japan.

Serological tests provide important confirmatory evidence for primary and secondary syphilis. However, the interpretation of serological data may be extremely complex in some cases. We describe here the occurrence of the prozone phenomenon (false-negative test) in a patient with secondary syphilis.

CASE REPORT

A 37-year-old woman presented with a rash on the palms, which had been present for 1 week. She reported that approximately 4 weeks before presentation, she had had sexual intercourse with a male partner who had a history of a similar rash. She had undergone renal transplantation, because of terminal renal failure due to chronic glomerulonephritis, 2 years before and was maintained on cyclosporine at 5 mg/kg and prednisolone at 10 mg daily. Examination revealed multiple erythematous macules and papules bilaterally on the palms (Fig. 1). Her laboratory test results were essentially non-contributory, including normal kidney functions, a negative enzyme immunoassay for human immunodeficiency virus (HIV), a negative venereal disease research laboratories (VDRL) test, and a normal cerebrospinal fluid examination. A check for the prozone phenomenon was requested and the VDRL test first became positive at a dilution of 1:8, remaining positive up to a titer of 1:128 (Table I). The fluorescent *Treponema pallidum* antibody-absorption test was positive. The patient was successfully treated with oral penicillin 1,500 mg daily for 4 weeks. Follow-up VDRL 3 months later was positive at a titer of 1:2 (Table I).

DISCUSSION

Laboratory diagnosis of syphilis can be made with dark-field microscopic examination or serological testing. Two basic types of humoral antibodies are stimulated by infection with *Treponema pallidum*: non-specific antibodies directed against diphosphatidyl glycerol (cardiolipin) and specific treponemal antibodies. The standard test currently in use for detection of anti-cardiolipin antibodies is the VDRL test, which is an easily quantified slide flocculation test. The use of non-treponemal serological tests such as the VDRL test and the rapid plasma reagin (RPR) test is widely accepted as an effective screening strategy for the detection of syphilis. Furthermore, the quantitative titer of the VDRL test is quite useful in following the patient's response to therapy. However, in some clinical situations difficulty in diagnosis results in misidentification of the true disease state despite the use of highly accurate tests (1). Biological false-positive results have been reported in many conditions such as hepatitis, systemic lupus erythematosus, and also in pregnancy (2, 3). On the other hand, false-negative results may occur when the patient is tested long after treatment, during late-latent syphilis, or as a result of the prozone phenomenon.

The prozone phenomenon is an immunological event seen when an excess of antibodies in the serum being tested prevents the formation of the antibody-antigen complex necessary to visualize a positive flocculation or agglutination reaction (4). This phenomenon has been reported with cryptococcal antigen testing (5), pregnancy testing (6, 7), HIV testing (8), and non-treponemal serological testing (9). The prozone phenomenon is said to occur in approximately 2% of cases of primary or secondary syphilis when VDRL or RPR tests are used (10). As shown in our case, syphilitic infection may be hidden in those patients whose serologic results are rendered negative by the prozone phenomenon. Recently, Jurado et al. (11) described the occurrence of the prozone phenomenon in HIV-positive individuals with secondary syphilis and proposed that B-cell hyperresponsiveness in HIV infection might cause the higher incidence of prozone phenomenon in these patients. In our case, continuous immunosuppression induced by cyclosporine and prednisolone may have led to B-cell dysfunction and higher non-treponemal serological titers. We recommend that serum dilution should be performed to evaluate the possibility of a false-negative result caused by the prozone phenomenon for any patient with negative serological results, in whom the clinical setting strongly suggests the presence of syphilis. Furthermore, the additional use of standard titration tests based on complement consumption (Wassermann test) should be considered.

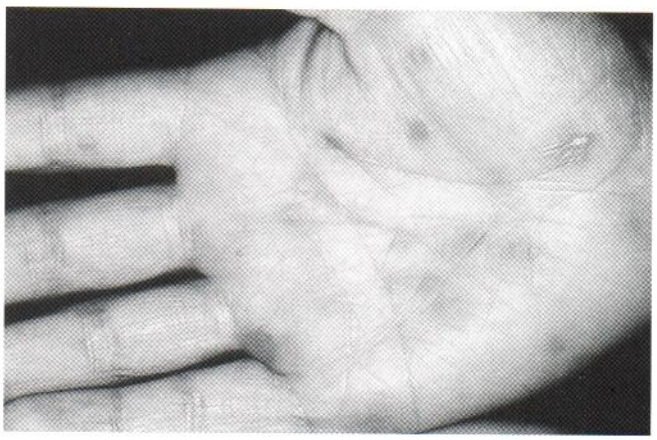

Fig. 1. Papulosquamous rash on the right palm.

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Table I. *VDRL test results*

Sera from the patient were titrated by doubling dilutions. –, non-reactive test; +, reactive test.

Sample date	Reciprocal titer of serum								
	1	2	4	8	16	32	64	128	256
April 28	–	–	–	+	+	+	+	+	–
May 9	–	–	+	+	+	+	–	–	–
June 6	+	+	+	+	–	–	–	–	–
July 4	–	+	–	–	–	–	–	–	–
July 25	+	+	–	–	–	–	–	–	–

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