

Immunosuppression in Patients with Syphilis and Problems of Human Immunodeficiency Virus Infection

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An investigation of the induced suppression and cytotoxicity of T lymphocytes, carried out in 57 patients with different forms of syphilis, has made it possible to find some reasons for the depression of cell-mediated immunity (CMI) in patients with early syphilis. The analysis of the immunoreaction of patients with different forms of syphilis clarifies the influence of the human immunodeficiency virus (HIV) on the dynamics and formation of syphilis manifestations.

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The role played by sexually transmitted diseases (STD) in the spread of the immunodeficiency virus (HIV) is obvious (1). In a revision in 1993 of the European AIDS Surveillance case definition, the pathology induced by sexually transmitted disease agents is considered (2). The syphilitic infection and its changes are of great interest to the investigators; these changes express themselves in an unusual development of the disease, therapy inefficiency, negative serological tests, etc, under the influence of HIV infection (3–5). Besides, the immune reaction analysis of different forms of syphilis is of interest. The interpretation of immunological changes can be an important aspect due to the imitation of other diseases by syphilis, including AIDS (6). In this connection, the analysis of immune responses during syphilis infection and the definition of its correction and dynamics are of great interest, taking into consideration the possibility of HIV infection.

We have analysed the induced suppression and cytotoxicity of T lymphocytes in patients with syphilis with respect to the diagnostics and immunopathology of the disease.

MATERIALS AND METHODS

Fifty-seven patients with syphilis, aged 20–60 years, were investigated at the clinic of skin and venereal diseases of the Kuban Medical Institute (Krasnodar, Russian Federation): 10 patients with primary syphilis, 20 patients with secondary syphilis, 16 patients with early latent syphilis and 11 patients with late latent syphilis. The diagnosis of primary and secondary syphilis was determined on the basis of the characteristic clinical manifestation of syphilis, positive Wassermann tests, and, if necessary, positive fluorescent treponemal antibody-absorption tests, and/or the presence of *Treponema pallidum* on dark-field microscopy. Early latent and late latent syphilis were diagnosed in accordance with the WHO recommendations (7).

The immunological investigations were carried out before the beginning of treatment. The suppressive activity of T cells was induced according to the method of Mehra et al. (8). Mononuclear cells from syphilis patients with normal mononuclear cells – at a density of 2.5×10^4 sorted cells/ 10^5 normal mononuclear cells – were cultured in

triplicate in RPMI 1640 containing 10% heat-inactivated pooled human AB serum. The cultures were stimulated with: a) PHA (2.5 µg/ml Difco, USA); b) cultivable treponemes biotype Stavropol (60 µg/ml, the Stavropol scientific research institute of vaccines and sera, Russian Federation); c) a mixture of cultivable treponemes and PHA; d) no additions. For assaying suppression of the mitogenic response by cultivable treponemes the culture plates were incubated for 3 days, and 18 h before harvest, 1 µg/ml of ^3H -thymidine (specific activity 2 Ci/mmol, Amersham International plc, Great Britain) was added. The ratio of the mean incorporation of ^3H -thymidine in triplicate cultures in the presence and absence of mitogen or antigen was taken as a measure of lymphocyte stimulation. The suppression of the PHA mitogenic response of lymphocytes by the presence of cultivable was expressed as:

$$\% \text{ suppression} = \left(1 - \frac{\text{cpm, cultivable treponemes} + \text{PHA}}{\text{cpm, PHA alone}} \right) \times 100.$$

The level of suppression above 10% was taken as suppression index.

T cell-mediated cytotoxicity was carried out according to the method of Woan & McGregor (9). The cultivated line of the cells produced from tissue of human amnion served as a target (10). The induction of the cytotoxicity of lymphocytes was carried out with PHA (10 µg/ml Difco, USA) and cultivable treponemes biotype Stavropol (60 µg/ml, the Stavropol scientific research institute of vaccines and sera, Russian Federation). Cells were cultured in 1 ml RPMI 1640 containing 10% heat-inactivated pooled human AB serum at a rate of 20 lymphocytes per 1 cell-target during 24 h at 37°C, the culture of the cells was washed with the fresh medium, 0.02% Versen's solution was added, and the culture was transferred into suspension and tintured with 0.1% trypan blue, after which the quantity of living cells was counted.

The cell-mediated cytotoxicity was determined according to the formula:

$$\% \text{ cytotoxicity} = \left(1 - \frac{a}{b} \right) \times 100.$$

where *a* is the number of living cells of targets after addition of induced lymphocytes and *b* is the number of living cells of targets without addition of induced lymphocytes.

The results were recorded as mean ± SE.

RESULTS

The results of induced suppression activity and cytotoxicity of T lymphocytes are given in Table I. The investigation results testify that the enforced suppression activity of lymphocytes has been accompanied by cytotoxicity reduction of T cells. The suppression activity level of lymphocytes differed due to the form of syphilis. The expressed suppression activity of lymphocytes was found in patients with early syphilis; most clearly, the suppression is revealed in the case of primary and early latent syphilis. No induced suppression activity of lymphocytes was revealed in patients with late latent syphilis; on the contrary, the stimulation of proliferation of lymphocytes induced by cultivable treponemes was observed. In the same way, but in a less degree, the stimulation of proliferation of lymphocytes was

Table I. Induced suppressive activity and cytotoxicity of T lymphocytes in patients with syphilis

Subjects	Incorporation of ³ H-thymidine by lymphocytes in the presence of PHA, cultivable treponemes + PHA and % suppression			Cytotoxicity of T cells (%)	
	cpm, PHA	cpm, cultivable treponemes + PHA	% suppression	Induced by PHA	Induced by cultivable treponemes
Primary syphilis	35239 ± 845	23641 ± 1271	32.9 ± 4.1*	19.6 ± 0.8*	10.0 ± 0.6*
Secondary syphilis	32420 ± 552	265677 ± 1921	17.9 ± 5.8*	22.9 ± 0.7*	9.0 ± 0.4*
Early latent syphilis	25857 ± 537	18310 ± 767	28.7 ± 2.9*	19.9 ± 1.3*	9.1 ± 0.5*
Late latent syphilis	37450 ± 531	43648 ± 2063	-16.1 ± 5.3	44.8 ± 1.2	18.1 ± 0.9
Normal (n 20)	41624 ± 403	46746 ± 1376	-12.5 ± 3.4	46.0 ± 1.2	3.4 ± 0.4*

Note. When determining % suppression, *p* was calculated relative to normal. * = *p* < 0.001

Note. When determining % cytotoxicity at induction of PHA, *p* was calculated relative to normal. * = *p* < 0.001. When determining % cytotoxicity at induction of cultivable treponemes, *p* was calculated relative to patients with late latent syphilis. * = *p* < 0.001

revealed in healthy persons by the induction of cultivable treponemes.

The investigation of cytotoxicity made it possible to reveal the difference between the lytic activity of lymphocytes of early and late syphilis induced both by specific and non-specific stimulators. The cytotoxicity of T lymphocytes induced by PHA is reduced in patients with early forms of syphilis, as compared with the cytotoxicity of lymphocytes in healthy persons and patients with late latent syphilis. The cytotoxicity is reduced equally in patients with primary, secondary and early latent syphilis. The cytotoxicity of lymphocytes induced by cultivable treponemes is reduced in patients with early forms of syphilis, as compared with that in patients with late latent syphilis.

DISCUSSION

In my opinion, the revealed increase of the suppression activity of lymphocytes in the case of primary, secondary and early latent syphilis is the protective reaction preventing immune response exhaustion in the period of infection generalization. Along with the factors of plasma (11, 12), decrease of T lymphocytes (13), T cell subpopulations (14) and other factors, the suppression activity of lymphocytes is one of the main reasons for the depression of cell-mediated immunity (CMI), including its effector link. The increase of the functional activity of lymphocytes induced by treponemal antigen in the case of late latent syphilis testifies, instead to CMI activation.

The revealed CMI depression resembles the immunological changes in HIV infection (15, 16); in this connection, the diagnostic testing for syphilis should be carried out with patients with immunodeficiency both in the presence and absence of antibodies to HIV. Special attention should be paid to early latent syphilis without clinical symptoms of the disease.

Despite of the fact that a defect in the CMI in syphilis has the secondary character, besides specific therapy, in my opinion, immunocorrective therapy proves its value, especially when there is an association of syphilis and HIV infection. In such cases the restoration of disturbed CMI should stipulate the

following circumstances. Firstly, the tactics of immunocorrection should stipulate a blockade of T-suppressors to a considerable degree, not an activation of helper cells in view of the negative influence on latent infected CD4+ lymphocytes. Such a method was demonstrated in the experimental investigations by application of antibodies to CD8+ lymphocytes, preventing or changing the immunopathological process (17). Secondly, the revealed depression of the CMI effector link by early syphilis can also stipulate the use of interleukin-2 to promote the generation of cytotoxic lymphocytes. Taking into consideration the deficiency of production of CMI mediators in patients infected with HIV, such therapy is suitable also for patients infected simultaneously with *Treponema pallidum* and HIV.

HIV infection leads to the reduction of immunity to many infections, including *Treponema pallidum* (18, 19), which is why CMI and immunopathology of early, but not late forms of syphilis can characterize the associated syphilis-HIV infection. This is proved by the formation of malignant forms of syphilis (20), as well as general paralysis of the insane, otherwise the quaternary syphilis (21) which is characterized by the absence of resistance to *Treponema pallidum* clinically and immunologically (negative skin tests, generalization of infection, etc) (22). At the same time, the clinical picture and the histology of the pathological process considered as gumma (23), the formation of which testifies to the high degree of resistance to *Treponema pallidum* (24), possibly once again justify the statement that syphilis is the great imitator of different diseases but do not reflect the essence of the immunopathology in syphilis-HIV infection.

Thus, an immune reaction analysis of different forms of syphilis contributes to our understanding of CMI depression and HIV influence on the pathogenesis of syphilitic damages.

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