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Original Article

Cellular immunity study of different prognoses in patients with early symptomatic syphilis

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Abstract: A total of 79 patients with complete follow-up data were obtained from 299 early symptomatic syphilis cases, between March 2014 and March 2018. There were 45 cases in the serum response group, 34 cases in the serum non-response group, and 64 normal volunteers served as the control group. Before treatment, levels of IL-4, IL-10, and IFN-γ in the serum response group were higher than those in the control group. Levels of IL-2, IL-4, IL-10, TNF-α, and IFN-γ in the serum non-response group were higher than those in the control group. Levels of IL-2, IL-4, IL-17A, TNF-α, and IFN-γ in the serum non-response group were higher than those in the serum response group. Twenty-four months after treatment, differences in decreases of IL-2 and IL-10 in the serum response group were statistically significant, compared with those before treatment. Differences in decreases of IL-2, IL-17A, and TNF-α in the serum non-response group were statistically significant, compared with those before treatment. IL-2, IL-4, IL-6, and IFN-γ levels in the serum non-response group were still higher than those in the serum response group. Levels of IL-2, IL-4, IL-6, and IFN-γ in the serum non-response group were still high after treatment. This may be one of the most important reasons for poor prognosis of early symptomatic syphilis.

Keywords: Early symptomatic syphilis, cytokine, cellular immunity, prognosis

Introduction

At present, epidemiological characteristics of syphilis show a rapid increase in incidence rates in China. Reporting rates have steadily increased. Gong et al. [1] found that the reported incidence of syphilis increased from 6.43/100,000 in 2000 to 32.86/100,000 in 2013, with an average annual growth rate of 13.37%. As incidence of syphilis continues to rise, incidence of treatment failure in syphilis patients has also significantly increased. In patients whose RPR titers continue to be positive, serum and clinical symptoms are repeatedly difficult to cure. They may even develop into advanced syphilis. This places a heavy burden on individuals, families, and society. Cellular immunity has been closely related to occurrence, development, and outcomes of syphilis [2]. Exploring the causes of treatment failure of syphilis and determining whether its occurrence is related to cellular immune dysregulation or immunosuppression, the Department of Dermatology, The First People's Hospital of Wujiang District, Suzhou, and the Department of Dermatology, The 904th Hospital of the People's Liberation Army Joint Service Support Force, designed and tested cellular immunological indicators of patients with early symptomatic syphilis after standard treatment.

Material and methods

Research objects

After examination and approval by the Medical Ethics Committee, 299 cases of early symptomatic syphilis without treatment, diagnosed by the Dermatology Department of the two hospitals, from March 2014 to March 2018 (all patients were diagnosed by RPR+TPPA), were selected. Serum samples were collected. Inclusion criteria: Patients with early symptomatic syphilis newly diagnosed. All were from the Dermatology Clinic; In line with the original Ministry of Health's early symptomatic syphilis (Phase I, Phase II) diagnostic criteria (WS 273-2007). Exclusion criteria: Early latent syphilis;

Malignant tumors; Autoimmune diseases; Those that were immunized within half a year; Those that had used hormones or immunomodulators within half a year; Patients with other infectious and sexually transmitted diseases. Treatment programs: After initial diagnosis, the patients were injected benzathine penicillin at G 2.4 million units on both sides of the buttocks muscle, once a week, for 3 consecutive weeks. All patients were followed up at 3, 6, 9, 12, 18, and 24 months after treatment. Serum RPR was reviewed and clinical manifestations and serum RPR titers were observed. Grouping: After 3 months of follow-up treatments, if the rash disappeared or if the RPR titer dropped greater than or equal to 2 dilutions or turns negative, these patients were included in the serum response group. If the RPR titer dropped less than 2 dilutions, it was judged that the serum did not respond. These patients were included in the serum non-response group (due to the principle of RPR test design and RPR titer change of less than 2 dilutions may not have any significance). If the serum response group had an increase in serum RPR titers above 2 dilutions during the 2-year follow-up period, they were classified in the serum non-response group. Elimination of primary syphilis with RPR titers of less than 1:4 was set. Both groups required no unclean sexual behavior during treatment and follow-ups. Seventy-nine patients that completed the 2-year follow-up and reviewed relevant cytokines were enrolled before March 2016. They were followed up until March 2018. Of these, there were 45 patients in the serum response group, including 20 males and 25 females, with an age distribution ranging from 19 to 68 (mean 34.1±12.6 years old). The median age was 36 years. There were 34 patients the in serum non-response group, including 16 males and 18 females, with an age distribution ranging from 23-62 years (mean 33.9±12.8 years). The median age was 38 years. At the same time, patients that underwent a physical examination were collected as the healthy control group. The total number was 64 (blood TPPA, RPR, and HIV antibody screening tests were negative, no history of autoimmune diseases). There were 36 males and 28 females, aged 18-49 (mean 33.1±10.6 years), with a median age of 34 years.

Research design

The current study prospective in nature. This study detected peripheral cytokine levels in patients with early symptomatic syphilis before standard treatment (divided into the serum response group and serum non-response group). They were followed-up for 2 years. Next, peripheral blood cytokine levels were reviewed after treatment, analyzing, comparing, and exploring: 1) Understanding cellular immune status during the pathogenesis of syphilis through the comparison of cytokine levels during the onset period and after treatment; and 2) Understanding the cellular immunology basis of different prognoses after syphilis treatment, comparing cytokine levels between the two groups.

Detection indicators and methods

Patients with early symptomatic syphilis were tested for peripheral blood cytokines, including IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and IFN-γ, before and after treatment, along with the healthy control group. Detection methods: A total of 2 mL of venous blood was collected in a sterile dry test tube. It was immediately centrifuged at 4,000 r/min for 15 minutes to obtain serum. It was then stored at -20°C in a freezer for testing. The human Th1/Th2 cytokine kit II for quantitative determination of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and IFN-γ is a product of the American BD company. The BD-CBA flow multiplex protein quantification technique was used for determination. The protocol was in full accord with reagent and instrument specifications.

Statistical analysis

Data was statistically analyzed using SPSS 21.0 statistical software package. Measurement data are expressed as mean ± standard deviation (±s). Student's t-test was used to compare the two means between groups. All statistical analyses were performed by two-sided tests. The test level is $\alpha=0.05$, with $P<0.05$ indicating significant differences.

Results

Comparison of serum cytokine levels in patients with early symptomatic syphilis before and after treatment

Compared with the healthy control group, all 299 patients with early symptomatic syphilis had higher IL-2, IL-4, IL-10, TNF-α, and IFN-γ levels, before treatment, than the healthy control

Table 1. Comparison of all patients with early symptomatic syphilis, compared with the healthy control group (±s, pg/ml)

	Pre-treatment of early symptomatic syphilis (n=299)	Healthy control group (n=64)	*t*	*P*	Normal reference value
IL-2	4.12±3.56	2.91±1.90	2.643	0.009*	<3
IL-4	3.79±3.69	2.48±1.62	2.779	0.006*	<3.5
IL-6	4.18±4.81	3.00±1.63	1.941	0.053	<8.5
IL-10	3.16±3.42	1.55±0.46	3.662	0.000*	<7
IL-17A	12.57±17.98	16.11±18.47	-1.423	0.156	<30
TNF-α	3.02±6.25	1.94±1.38	2.192	0.037*	<3.5
IFN-γ	3.30±4.72	1.95±1.29	2.261	0.024*	<4

*P<0.05.

Table 2. Comparison of the serum response group with the healthy control group before treatment (±s, pg/mL)

	Pre-treatment of Serum response group (n=45)	Healthy control group (n=64)	*t*	*P*
IL-2	3.73±2.86	2.91±1.90	1.812	0.073
IL-4	3.34±2.55	2.48±1.62	2.158	0.033*
IL-6	4.21±5.42	3.00±1.63	1.687	0.095
IL-10	2.74±1.70	1.55±0.46	4.566	0.000*
IL-17A	10.28±10.44	16.11±18.47	-2.095	0.039*
TNF-α	2.62±3.82	1.94±1.38	1.315	0.191
IFN-γ	2.70±1.49	1.95±1.29	2.787	0.006*

*P<0.05.

Table 3. Comparison of the serum non-response group with the healthy control group before treatment (±s, pg/mL)

	Pre-treatment of Serum non-response group (n=34)	Healthy control group (n=64)	*t*	*P*
IL-2	6.79±8.13	2.91±1.90	2.747	0.009*
IL-4	6.41±8.42	2.48±1.61	2.701	0.011*
IL-6	5.53±7.76	3.00±1.63	1.878	0.069
IL-10	4.51±7.54	1.55±0.46	2.289	0.029*
IL-17A	23.38±36.56	16.11±18.47	1.087	0.283
TNF-α	6.64±15.11	1.94±1.38	2.480	0.015*
IFN-γ	6.41±11.01	1.95±1.29	2.352	0.025*

*P<0.05.

group. Differences were statistically significant (P<0.05), **Table 1**. Before treatment, 45 patients in the serum response group had higher IL-4, IL-10, and IFN-γ levels than the healthy control group. Differences were statistically significant (P<0.05), **Table 2**. Before treatment, 34 patients in the serum non-response group had higher IL-2, IL-4, IL-10, TNF-α, and IFN-γ levels than the healthy control group. Differences were statistically significant (P<0.05), **Table 3**.

Comparison of cytokine levels in serum response group during the onset period and after treatment. IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α, and IFN-γ levels decreased in the serum response group at 24 months after treatment. Decreases in IL-2 and IL-10 were statistically significant, compared with that before treatment (P<0.05), **Table 4**.

Comparison of cytokine levels in the serum non-response group during the onset period and after treatment

After treatment, the serum non-response group showed a downward trend in IL-2, IL-4, IL-10, IL-17A, TNF-α, and IFN-γ levels at 24 months, including IL-2 and IL-17A. TNF-α was significantly decreased, compared with that before treatment. Differences were statistically significant (P< 0.05), **Table 5**.

Comparison of cytokine levels between the serum response group and serum non-response group before and after treatment

Cytokines IL-2, IL-4, IL-17A, TNF-α, and IFN-γ were significantly different between the two groups, before treatment (P<0.05), **Table 6**. After treatment, cytokines IL-2, IL-4, IL-10, IL-17A, TNF-α, and IFN-γ in the two groups showed a downward trend compared with that before treatment. Differences in IL-2, IL-4, IL-6, and IFN-γ between the two groups after treatment were statistically significant (P<0.05), **Table 7**.

Discussion

At present, cellular immunity research concerning the prognosis of syphilis is not rigorous.

Table 4. Comparison of the serum response group before and after treatment (±s, pg/mL)

	Serum response group (n=45)		*t*	*P*
	Before treatment	24 months after treatment		
IL-2	3.73±2.86	2.64±1.50	2.223	0.031*
IL-4	3.34±2.55	2.88±2.07	1.157	0.254
IL-6	4.21±5.42	3.58±2.53	0.661	0.512
IL-10	2.74±1.70	2.12±1.28	2.066	0.045*
IL-17A	10.28±10.44	9.15±6.30	0.595	0.555
TNF-α	2.62±3.82	2.29±1.66	0.511	0.612
IFN-γ	2.70±1.49	2.34±1.36	1.192	0.240

*P<0.05.

Table 5. Comparison of the serum non-response group before and after treatment (±s, pg/mL)

	Serum non-response group (n=34)		*t*	*P*
	Before treatment	24 months after treatment		
IL-2	6.79±8.13	4.45±3.82	2.902	0.007*
IL-4	6.41±8.42	5.62±6.05	0.851	0.401
IL-6	5.53±7.76	6.94±9.34	-0.855	0.399
IL-10	4.51±7.54	3.15±3.48	1.839	0.075
IL-17A	23.38±36.56	9.17±7.05	2.525	0.017*
TNF-α	6.64±15.11	3.58±6.83	2.059	0.047*
IFN-γ	6.41±11.01	4.02±2.74	1.611	0.117

*P<0.05.

Normally, it is not staged according to the course of the disease. The control is not scientific, especially research that is mostly concentrated on serofast. For example, Xie et al. [3] tested concentrations of peripheral blood cytokines in 32 patients with serofast syphilis, showing that IL-2 and IL-12 levels were lower than the healthy group. IL-4 and IL-10 levels were higher than the healthy group. Zhao et al. [4] detected peripheral blood Treg cells and Th17 cells in 26 patients with serofast syphilis. Treg cells were significantly higher than the normal control group. Th17 cells were significantly lower than the normal control group. Sun et al. [5] detected $CD4^+CD25^+$ regulatory T-cells and IL-17 in peripheral blood of 18 patients with serofast syphilis. Compared with healthy controls, they found that immunosuppression caused by increased expression of $CD4^+CD25^+$ regulatory T-cells may be related to serofast syphilis. IL-17 expression levels may not be related to serofast syphilis. These cellular immunological studies on serofast syphilis were designed to detect peripheral blood immune cell levels after serofast in patients with syphilis. They can only indicate the status of cellular immunity in patients with syphilis during serofast. This research is lagging and cannot reflect the cellular immune status of the initial infection with Treponema pallidum. These studies did not strongly prove whether cellular immune disorder was the “effect” or “cause” of serofast. Most of them compared serofast syphilis patients with healthy controls. They did not compare them with non-serofast syphilis patients. Thus, these studies lacked scientific rigor and persuasiveness. Nie et al. [6] examined levels of serum IL-2, IL-10, and TNF-α in 55 patients with early symptomatic syphilis, comparing them with 65 normal people as controls. Levels of IL-2, IL-12, and TNF-α were significantly higher in those patients than in the normal group. Levels of IL-2 and TNF-α in patients with primary syphilis were higher than those in patients with secondary syphilis. Levels of IL-10 in patients with secondary syphilis were higher than those in patients with primary syphilis. IL-2 and IL-10 were negatively correlated, while TNF-α and IL-2 were positively correlated. This study only examined peripheral blood cytokine levels in patients with early symptomatic syphilis. It did not compare different prognoses after standard treatment, only comparing with healthy people. Thus, it cannot explain the impact of cellular immunity on different prognoses of early symptomatic syphilis. To this end, the current study differentiated the early syphilis serum response group and serum non-response group, according to prognosis design. This study detected relevant cytokines, before and after treatment, aiming to explore the cellular immune rule of early symptomatic syphilis.

Present results showed: 1) In the 299 large samples of early syphilis patients spanning 4 years, IL-2, IL-4, IL-10, TNF-α, and IFN-γ levels were significantly higher than those in the healthy control group before treatment ($P<0.05$). This suggests that patients with early symptomatic syphilis induced cellular immune responses due to TP infections. Concentrations of Th1 cytokines and Th2 cytokines were increased; 2) Before treatment, IL-4, IL-10, and IFN-γ levels in the serum response group were

Table 6. Comparison of the serum response group with serum non-response group before treatment (±s, pg/mL)

	Serum response group before treatment (n=45)	Serum non-response group before treatment (n=34)	*t*	*P*
IL-2	3.73±2.86	6.79±8.13	-2.345	0.022*
IL-4	3.34±2.55	6.41±8.42	-2.317	0.023*
IL-6	4.21±5.42	5.53±7.76	-0.889	0.377
IL-10	2.74±1.70	4.51±7.54	-1.530	0.130
IL-17A	10.28±10.44	23.38±36.56	-2.287	0.025*
TNF-α	2.62±3.82	6.64±15.11	-2.715	0.000*
IFN-γ	2.70±1.49	6.41±11.01	-2.239	0.028*

*P<0.05.

Table 7. Comparison of the serum response group with serum non-response group after treatment (±s, pg/mL)

	Serum response group after treatment (n=45)	Serum non-response group after treatment (n=34)	*t*	*P*
IL-2	2.64±1.50	4.45±3.82	-2.892	0.005*
IL-4	2.88±2.07	5.62±6.05	-2.530	0.016*
IL-6	3.58±2.53	6.94±9.34	-2.046	0.048*
IL-10	2.12±1.28	3.15±3.48	-1.834	0.070
IL-17A	9.15±6.30	9.17±7.05	-0.012	0.990
TNF-α	2.29±1.66	3.58±6.83	-1.082	0.287
IFN-γ	2.34±1.36	4.02±2.74	-3.578	0.001*

*P<0.05.

higher than those in the healthy control group (P<0.05). Serum non-response group IL-2, IL-4, IL-10, TNF-α, and IFN-γ levels were higher than those in the healthy control group (P<0.05). IL-2, IL-4, IL-17A, TNF-α, and IFN-γ levels were higher in the serum non-response group than in the serum response group before treatment (P<0.05). This suggests that untreated early symptomatic syphilis had a different cellular immune status in the serum non-response group and serum response group and that Th1-type immune responses and Th2-type immune responses in the serum non-response group were more significant; 3) At 24 months after treatment, IL-2, IL-4, IL-10, IL-17A, TNF-α, and IFN-γ levels in the serum response group and serum non-response group showed a downward trend. Compared with before treatment, differences in IL-2 and IL-10 in the serum response group were statistically significant (P< 0.05). Differences in IL-2, IL-17A, and TNF-α in the serum non-response group were statistically significant (P<0.05). However, IL-2, IL-4, TNF-α, and IFN-γ levels, after treatment, were still higher than the normal reference value. After treatment, IL-2, IL-4, IL-6, and IFN-γ levels in the serum non-response group were still higher than those in serum response group. Differences were statistically significant (P<0.05). This suggests that it is effective for TP treatment. In the serum response group, cytokines can return to the normal range and cellular immunity may return to the original state. However, cytokines in the serum non-response group were still higher than the normal reference value. Th1-type immune responses and Th2-type immune responses against TP still existed.

After TP invades the human body, the body will produce humoral immunity and cellular immunity. This shows a complex process in which the active phase and the stationary phase alternate. Although anti-TP specific antibodies in humoral immunity have a high titer, they cannot prevent the proliferation and spread of TP, indicating that the protective effects of specific antibodies are limited. Both systemic and local cellular immune responses play an important role in controlling TP infections. Studies have been conducted to determine the correlation between cellular immunity and TP infections, via various studies on peripheral blood and rash immune cells in patients with syphilis. Although conclusions are not identical, they all believed that there are cellular immune imbalances or immunosuppression in patients with syphilis. Studies have suggested that the cellular immunity of patients with syphilis is abnormal. The balance of Th1/Th2 cytokines in peripheral blood of patients with syphilis is dysregulated. An imbalance of cellular immunity can increase the chances of infections with TP. At the same time, it affects the development and outcomes of syphilis. Fitzgerald [7] proposed that Th1 cells predominate in primary syphilis and secondary syphilis is transformed into the predominance of Th2 cells. It is believed that Th1 cell-mediated delayed-type hypersensitivity in $CD4^+$ T lymphocytes is the main mechanism for clearing TP *in vivo*. Zhou et al. [8] observed that expression of Th1 type cytokines in early syphilis lesions was positively correlated with the

negative conversion of syphilis RPR testing. Van Voorhis et al. [9] found that primary syphilis skin lesions were rich in mRNA of IL-2, IFN-γ, and IL-12, while mRNA of Il-4 was not measured. They believed that early syphilis local immunity is dominated by Th1 immune response, while Th2 immune response is relatively suppressed. Podwinska et al. [10] showed that primary syphilis patients have obvious advantages in Th1 cells and that lymphocytes have the greatest ability to produce Th1 cytokines. As the disease progresses, Th1 type cytokines gradually decrease and Th2 type cytokines gradually increase. Cellular immunity of the body is inhibited, causing the prolongation of the course of syphilis. In the late stage of syphilis, the superiority of Th2 cells is more prominent. Secretion of IL-10 reaches the maximum. Based on current findings, it is believed that, in the early stages of TP infections, Th1-type immune responses (representative cytokines IL-2, TNF-α, IFN-γ) and Th2-type immune responses (representative cytokines IL-4, IL-6, IL-10) are initiated at the same time. Since IL-2 is higher than the normal reference value, Th1-type immune responses are dominant. The main effect of Th1-type immune responses is enhanced phagocytic-mediated immunity against infections. The main effect of Th2 type immune response is induction and promotion of B-cell-mediated humoral immunity. In this study, Th1 type cytokines, IL-2 and IFN-γ, and Th2 type cytokines, IL-10 and IL-4, in the serum response group were elevated without treatment. This indicates that, in the early period of TP infections, both cellular and humoral immunity are initiated simultaneously. After treatment, it returned to the normal range, showing a dynamic balance of Th1/Th2 recovery. In the serum non-response group, Th1 type cytokines, IL-2, TNF-α, and IFN-γ, and Th2 type cytokine, IL-4, were higher than the reference value after treatment. Th1 type cytokines, IL-2 and IFN-γ, and Th2 type cytokines, IL-4 and IL-6, were higher than in the serum response group. Results suggest that cellular immunity of the serum non-response group was persistent. Compared with cytokines before treatment, Th1 type cytokines, IL-2 and TNF-α, were significantly decreased ($P<0.05$), while Th2 type cytokines, IL-4, IL-6, and IL-10, did not show a significant decrease. Even IL-6 concentrations increased. This suggests that Th1/Th2 imbalances in the serum non-response group drifted toward the Th2 type of immunity, because Th2 type cells can stimulate B-cell proliferation and produce immunoglobulin. This often results in the persistence of humoral immunity, causing the serum not to respond. During the follow-up period of the serum non-response group, serum RPR titer decreased by less than 2 dilutions. Syphilis treatment response was poor. The course of disease was prolonged.

The Th17 cell subset is a class of $CD4^+$ T-cells, different from Th1 and Th2, which secretes IL-17. Studies have shown that IL-17 has dual features of anti-infection and inflammation promotion [11, 12]. IL-17 has important anti-infective effects in both innate and adaptive immunity. However, IL-17 is also a key factor in the tissue damage of infected organs [13]. In patients infected with spirochetes, IL-17 appears to be preferentially expressed [14]. Th17 cells and Th1 cells coordinate with each other in the inflammatory reaction, mediating the occurrence and development of inflammation. Th17 cells produce faster than Th1 cells and play a leading role in the early stages of inflammatory response. Th1 cells play a role in maintaining inflammatory response. Th17 cells may be involved in the early clearance of Treponema pallidum [15]. In this study, IL-17a in the serum non-response group, after treatment, was significantly different from that before treatment ($P<0.05$), suggesting that Th17 cell-mediated immune response had a certain defect in the process of TP clearance after TP infections in the serum non-response group.

The highlights of this study, compared with previous studies, are as follows: 1) This study included more comprehensive cytokines and large data samples. Previous studies rarely included more than 79 patients [3, 6, 16]; and 2) Levels were compared with not only the healthy control group, but also the serum response group and serum non-response group, including before and after treatment. Huang [16] detected concentrations of peripheral blood-related cytokines in 38 patients with serofast syphilis, finding that their IFN-γ, IL-2, TNF-α, and IL-12 levels were lower than those of the untreated syphilis group, negative syphilis group, and control group. Levels of IL-10 and IL-4 were significantly higher than those of the untreated syphilis group, negative syphilis group, and control group. However, serofast often exceeds the time limit of early syphilis. The cur-

rent study of early syphilis cytokines is more clinically instructive. By exploring changes, the current study provides evidence for early indications of poor prognosis. This study did not distinguish between primary syphilis and secondary syphilis, because normally RPR titers of primary syphilis were not significantly increased. The number of patients in the serum non-response group was too small to be included in statistical analysis. Future studies should include more centers and larger samples for the serum response group and serum non-response group.

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Disclosure of conflict of interest

None.

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