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Autologous cytokine-induced killer (CIK) immunotherapy in a case of disseminated tuberculosis

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Abstract. A 23-year-old woman had dry cough, fever and chest tightness for 1 months. Through thoracic CT scan and serological examination, the patient was clinically diagnosed as disseminated tuberculosis. she was given anti-tuberculosis therapy combined with autologous cytokine-induced killer (CIK) immunotherapy. Through the close follow-ups we found that after immunotherapy Her condition would have a swift improvement and she do not appear liver damage after a large doses of antibiotic therapy. In conclusion, adjuvant autologous CIK immunotherapy is an effective approach for disseminated tuberculosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 83-86)*

Key words: CIK, disseminated tuberculosi, immunotherapy

Abbreviations

CIK, cytokine-induced killer; TB, tuberculosis; MDR-TB, multi-drug resistant tuberculosis; LYMPH, Lymphocyte count; ESR, Erythrocyte sedimentation rate; Alb, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TP, Total protein; CRP, C-reactive protein; PCT, Procalcitonin; α-IFN, α- Interferon; IL-2R, Interleukin-2 receptor; IL-6, , Interleukin-6

Introduction

Since the 1980s, there has been a trend of resurgence of tuberculosis (TB) epidemic in both developed and developing countries. One of the main reasons for the resurgence of TB epidemic is the epidemic of multi-drug resistant TB (MDR-TB) and AIDS, which has become a major obstacle to TB control. Because MDR-TB is not sensitive to a variety of anti-tuberculosis drugs, in addition to its high mutability, the existing conventional treatment means are more sluggish in the treatment of multi-drug resistance (MDR). Therefore, the development of new anti-tuberculosis drugs or discovery of new therapy is becoming a more and more urgent problem for humans.

Since autologous CIK immunotherapy can stimulate the body's immune function and have a special role of supportive treatment for the body (1-4), we use CIK immunotherapy in the treatment of tuberculosis. Here, we report one case of patient with disseminated tuberculosis that was improved rapidly after CIK immunotherapy.

Case report

A 23-year-old woman had dry cough, fever and chest tightness for 1 months. Admission examination: T: 39 ; P: 112 beats/min; R: 24 beats/min; BP: 106/60 mmHg. She was with fair spirit, but required

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a wheelchair into the ward for her poor mobility. The double-lung respiratory sounds were coarse, with obvious dry and moist crackles. CT scan showed that the diffuse distribution of small nodular shadows was visible in double lungs, with even size, density and distribution (Figure 1A,B). Blood routine and blood sedimentation examinations showed that the LYMPH was decreased, and the ESR was elevated (Table 1C). Tuberculosis culture was positive. Four pieces of acid-fast bacilli were found in 300 visions of sputum pictures (Table 1B). Cytokine assay showed that IL-2 receptor, IL-6, α-TNF and procalcitonin were all increased (Table 1C). Liver function tests found a low level of albumin (Table 1A). Meanwhile, serological examination showed that the HIV antibody was negative, and the tumor markers were normal. Therefore, the patient was clinically diagnosed as disseminated tuberculosis.

The patient was given anti-TB therapy combined with autologous CIK cell therapy. CIK cells were generated as described previously (5,6). Briefly, Ficoll-separated human peripheral blood mononuclear cells were prepared and incubated in RPMI1640 medium containing 100 ml·L^{-1} autologous

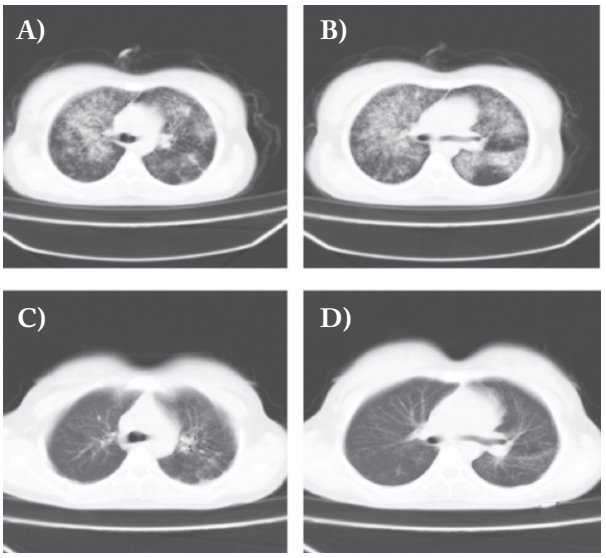

Fig. 1. Thoracic CT before (A,B) and after (C,D) CIK treatment. The time points of A and B are the initial examination (25days before the CIK treatment). The time points C,D are 1 month later after CIK treatment when the paitent leave hospital. A and B showed that the diffuse distribution of small nodular shadows was visible in double lungs, with even size, density and distribution.C and D showed that after CIK immunotherapy the lung texture become clear and the lesion significant absorption

Table 1. The time points of A and C are the 25days before CIK treatment, the day before CIK treatment and the day after CIK treatment. The time points B are the 25days before CIK treatment, the day before CIK treatment and one month later after CIK treatment when the paitent leave hospital. A: Some indicators of liver function, liver function improved after treatment and do not appear liver damage after large doses of antibiotic therapy. B: Before and after immunotherapy the chang of Sputum culture, sputum smear . C: Before and after immunotherapy the chang of LYMPH, ESR and Cytokines

A	Initial examination (25 days before the immunotherapy)	The day before immunotherapy	The day after immunotherapy
TP	58.8 g/L	64.7 g/L	81.3 g/L
Alb	25.8 g/L	29.5 g/L	47.1 g/L
AST	17 U/mL	15 U/mL	9 U/mL
ALT	11 U/mL	17 U/mL	17 U/mL
B	Initial examination (25 days before the immunotherapy)	The day before immunotherapy	Last examination (1 month after immunotherapy)
Culture	Positive	Positive	Negative
Smear	4/300 vision	5/300 vision	Not detected
C	Initial examination (25 days before the immunotherapy)	The day before immunotherapy	The day after immunotherapy
LYMPH	0.42*10^9/L	0.83*10^9/L	1.73*10^9/L
LYMPH%	9.1%	9.2%	33.1%
ESR	49 mm/H	39 mm/H	8 mm/H
IL-2R	6838 U/mL	4806 U/mL	742 U/mL
IL-6	17.6 pg/mL	6.2 pg/mL	<2 pg/mL
α-IFN	47.7 pg/mL	76.9 pg/mL	19.4 pg/mL
PCT	0.178 ng/mL	0.134 ng/mL	0.021 ng/mL
CRP	83.0 mg/L	46.3 mg/L	0.0 mg/L

plasma and various types of cytokines added according to the reported protocol with minor modifications (6). The final concentrations of the cytokines and antibody added were as follows: IFN-γ, 1000U·L-1; IL-2, 1000U·mL^{-1}(After 24 h); IL-1, 100U·mL^{-1}(After 24 h); mAb CD3, 100ng·mL^{-1} (After 24 h). Cells were incubated at 37 and fed every 2 days in fresh complete medium with IL-2 (1000U·mL^{-1}) at 2×10^{6} cells·mL^{-1}. When cultured for 10 days, taken out one third of the medium, concentrated into 100ml saline and injection to patients with 1*10^{6} U IL-2 to the patient together. The CIK cells was given every other day, with a total of three times for six days. The number of cells were 3.61*10^{9},4.52*10^{9} and 3.01*10^{9}. After treatment, the patient complained a substantial increase in the quality of sleep and the improvement of the appetite. At the second day, the patient underwent blood test of various biochemical, physiological and immunological indicators. The results showed that the LYMPH and Alb were both increased (Table 1 A,C); the ESR was decreased (Table 1C); various cytokines returned to normal values (Table 1C). At one month later after CIK treatment when the paitent discharged the sputum culture and sputum smear were both negative (Table 1B); CT scans showed clear lung texture and significant absorption in the lesion. The patient was able to walk normally when she was discharged. Her weight gained 5 kg (Table 1B). The skin was also found to be improved. A stain on the inner thighs also disappeared.

Discussion

First discovered by Schmidt-Wolf, et al (7) of American Standford University in 1991, CIK cell therapy is an immune therapy that is most widely used clinically (8-9). It mainly involves the acquisition of a group of CD3^{+} CD56^{+} double positive T cells through cytokines and in vitro culture, and kills tumor cells or pathogens by using the non-specificity of this group of cells (10). Through the summaries of its treatments of tumors, we discovered that CIK cells could secrete a large amount of cytokines during the treatment process, elevate patients' ratios of CD4^{+}/CD8^{+} and Th1/Th2 while reducing the proportion of Treg, and greatly stimulating the specific immune response of Th1 cells (1-4). This just inhibits the immune evasion mechanism of tuberculosis, thus enabling the body to regain the capacity of killing the tuberculosis (11-13).

In this case, the patient accepted an agreement involving close follow-ups so as to facilitate the observations on the possible progression of her disease in the CIK immunotherapy. Fortunately, her condition was improved rapidly, and through the close follow-ups we found that after immunotherapy she would have a swift improvement and do not appear liver damage after a large doses of antibiotic therapy. The success of the treatment of her disease convinced us that we can speed up the improvement of the patient's condition and elevate her life quality by using CIK immunotherapy to cure TB. Therefore, we believe that when the conventional therapy is carried out we can speed up the improvement of the TB patient's condition and enhance the paitent's life quality by using the CIK immunotherapy at the same time. So we believe that the CIK immunotherapy is an effective one for tuberculosis treatment.

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