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New attempt in tuberculosis treatment: autologous cytokine-induced killer after chemotherapy treatment failure in a case of multi-drug resistant tuberculosis (MTB)

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Abstract. A 32-year-old woman was diagnosed as pulmonary tuberculosis 15 years ago and recurred several times due to long-term nonstandard treatment. Drug sensitivity test indicated that multidrug-resistant tuberculosis had emerged and we determined relevant therapeutic schedule according to this result. However, it didn't show any amelioration of the disease after 3-month chemotherapy. We formulated 3-course CIK immunotherapy based on patient's condition. After 3 courses of immunotherapy, we found obvious amelioration of the patient's condition. And there was no recurrence during the follow-up in the past 3 years. Therefore, we considered that the CIK immunotherapy is an effective method for tuberculosis treatment and recurrence prevention. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 97-99)*

Key words: cell therapy, multi-drug resistant tuberculosis, CIK

Abbreviations
CIK, cytokine-induced killer; TB, tuberculosis; MDR-TB, multi-drug resistant tuberculosis

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).

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In the global tuberculosis report 2015 of WHO had report that in 2014, there were an estimated 480 000 new cases of MDR-TB worldwide, and approximately 190 000 deaths from MDR-TB. The report also report that only 50% of patients on MDR-TB treatment were successfully treated and the treatment methods of MDR-TB were still insufficient (1).

Since autologous CIK immunotherapy can stimulate the body's immune function and have a special role of supportive treatment for the body (2-4), we use CIK immunotherapy in the treatment of tuberculosis. Here, we report one case of chemotherapy treatment failure patient with MDR-TB that was improved after only CIK immunotherapy.

Case report

A 32-year-old woman with repeating cough and expectoration for 4 years was admitted to hospital in

March 2012 because of aggravation for half a year. Patient history: She was diagnosed as pulmonary tuberculosis 15 years ago and underwent a 2-month anti-tuberculosis therapy, but she stopped unauthorizedly due to the side effect and didn't receive any standard treatment. She was diagnosed as secondary pulmonary tuberculosis four years ago. She was given anti-tuberculosis treatment and still suffered from repeating cough and expectoration after the anti-tuberculosis course. The patient's cough and expectoration aggravated 3 years ago, coughed purulent sputum and was admitted to our hospital in March 2012. Examination on admission: T: 38°; P: 106 beats/min; R: 27 beats/min; BP: 110/65 mmHg; severely marasmus; weight: 40 kg; chest CT: uneven density in bilateral lung with partial densification and calcification, cavity in upper right lung (Figure 1A,B). Sputum smear and culture showed a tubercle-bacillus-positive result and drug sensitivity test indicated widespread multidrug-resistant tubercle bacillus (Table 1A,B,C); flow cytometry analysis found a higher percentage of B cells and Treg cells (Figure 1E). Therefore, the patient was diagnosed as widely multidrug-resistant pulmonary tuberculosis and given the appropriate chemotherapy based on susceptibility testing.

After 3 months treatment, there was no evident amelioration and the inspection results showed exacerbation of the patient's condition; persistent body weight loss and severe side effects such as violent vomiting occurred while using megadose of antibiotics; positive sputum smear and culture (Table 1A); flow cytometry showed a further decreasing percentage of CD4+ and CD8+ lymphocyte subsets as well as a further increasing percentage of B cells and Treg cells (Figure 1E). Because of the seriously illness and the failure of chemotherapy, we implemented the CIK cell with patient's informed consent and approval. The CIK cells were given every other day, with a total of three times for six days and these six days were a course. The patient's condition ameliorated obviously after a 3-course treatment of 90 days. And after the first course the sputum culture and sputum smear were both negative (Table 1A); We implemented a chest CT inspection for the patient after the third course of CIK immunotherapy and found pulmonary cavity was shrinking, patch and nodule in some aspects were absorbed by contrast with those before CIK therapy (Figure 1 C,D). At the same time, through the follow-up we found that CD4+ and CD8+ lymphocyte subsets were increased and the B cell and Treg lymphocyte subsets were decreased after each immunotherapy (Figure 1E). There was no recurrence during the follow-up in the past 3 years.

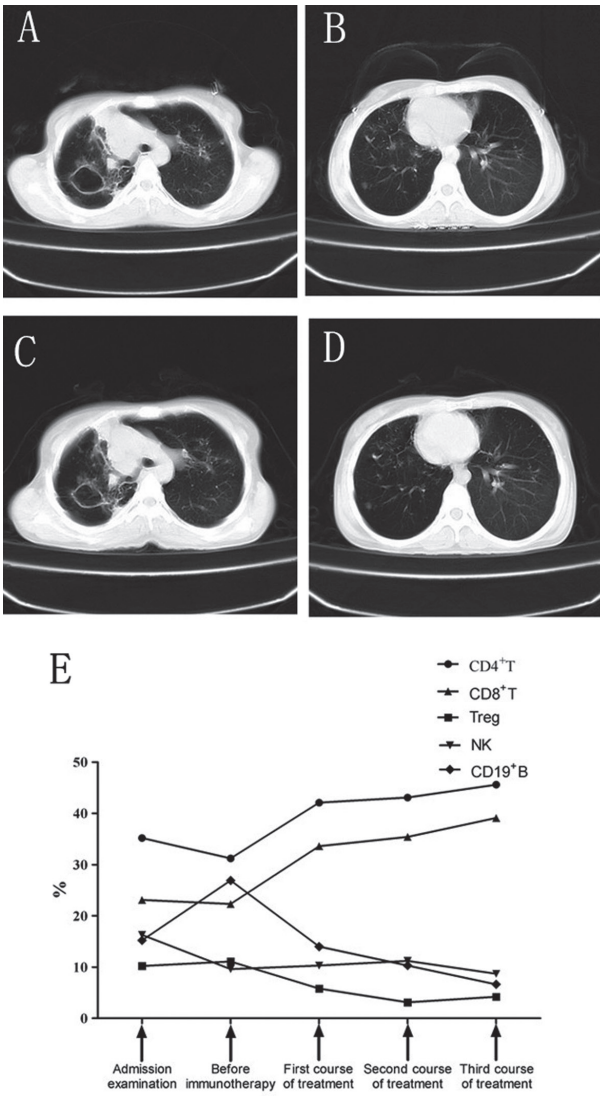

Fig. 1. Thoracic CT (A,B,C,D) and the changes of lymphocyte subsets (E). The time points of A and B are the initial examination. The time points C,D are 1 month later after the third course of CIK immunotherapy. Compare with before and after CIK treatment, the pulmonary cavity was shrinking, the patch and nodule in some aspects were absorbed E.

Discussion

First discovered by of American Standford University in 1991 (5), CIK cell therapy is an immune

Table 1.

sTable 1A.Bacteriological examination

Test items	Admission examination	Before immunotherapy	First course of treatment	Second course of treatment	Third courseof treatment
Smear	Positive(3+)	Positive(3+)	Not detected	Not detected	Not detected
Culture	Positive	Positive	Negative	Negative	Negative

sTable 1B.Bacterial identification

Mycobacterium tuberculosis classification	Human-type Mycobacterium tuberculosis

sTable 1C.Bacteriological susceptibility testing

Name of antibiotics	Results	Name of antibiotics	Results
Streptomycin	Resistance	Levofloxacin	Resistance
Isoniazid	Resistance	Aminosalicylate	Sensitive
Rifampicin	Resistance	Protionamide	Resistance
Ethambutol	Resistance	Amikacin	Sensitive

therapy that is most widely used clinically. 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 (6). 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. This just inhibits the immune evasion mechanism of tuberculosis, thus enabling the body to regain the capacity of killing the tuberculosis. In our earlier research, we had found the CIK immunotherapy was safe, and combined with chemotherapy can speed up the improvement of the disease (7).

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 and through the close follow-ups we found that there was no recurrence until now. The success treatment of her disease convinced us the CIK immunotherapy is an effective method for tuberculosis treatment and recurrence prevention.

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Human and animal rights:
This study was performed with the approval of the local ethical committee.

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