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Cord Blood-Derived Cytokine-Induced Killer Cellular Therapy Plus Radiation Therapy for Esophageal Cancer

A Case Report

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Abstract: Esophageal cancer is a serious malignancy with regards to mortality and prognosis. Current treatment options include multimodality therapy mainstays of current treatment including surgery, radiation, and chemotherapy. Cell therapy for esophageal cancer is an advancing area of research.

We report a case of esophageal cancer following cord blood-derived cytokine-induced killer cell infusion and adjuvant radiotherapy. Initially, she presented with poor spirit, full liquid diets, and upper abdominal pain.

Through cell therapy plus adjuvant radiotherapy, the patient remitted and was self-reliant. Recognition of this curative effect of sequent therapy for esophageal cancer is important to enable appropriate treatment.

This case highlights cord blood-derived cytokine-induced killer cell therapy significantly alleviates the adverse reaction of radiation and improves the curative effect. Cell therapy plus adjuvant radiotherapy can be a safe and effective treatment for esophageal cancer.

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Abbreviations: CB-CIK = cord blood-derived cytokine-induced killer, KPS = karnofsky performance status, PET/CT = positron emission tomography/computed tomography, UICC = Union for International Cancer Control.

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INTRODUCTION

Esophageal cancer is a serious malignancy with regards to mortality and prognosis. It is a growing health concern that is expected to increase in incidence over the next 10 years.[1] With the increased prevalence of gastroesophageal reflux disease and obesity in developed nations, the incidence of esophageal adenocarcinoma has dramatically increased in the past 40 years. Current treatment options include multimodality therapy mainstays of current treatment including surgery, radiation, and chemotherapy.[1] Cell therapy for esophageal cancer is an advancing area of research. In this article, we describe the case of an esophageal cancer patient following cord blood-derived cytokine-induced killer (CB-CIK) cell infusion plus adjuvant radiotherapy, and she recovered well in order to evaluate the feasibility, safety, and efficacy of this technique.

PATIENT AND METHODS

Patient and Procedures

A 75-year-old woman with a medical history of hypertension >10 years, Parkinson >8 years, and diabetes for 2 years presented with poor spirit, full liquid diets, weight loss, and upper abdominal pain. The patient was admitted to hospital. According to the Karnofsky performance status (KPS) she scored 60 points. The biochemical analysis was performed, which showed that the carcinoembryonic antigen was 4.98 ng/mL and ferritin was 184.2 ng/mL (reference range, 12−150 ng/mL). Electronic ultrasonic gastroscopy showed esophageal tumor size that was 2.5 × 2 cm involving the bottom of the stomach; the middle esophagus was jammed with apophysis lesions (Figure 1A and B). Computed tomography showed esophagus thickening (Figure 2). A provisional diagnosis of esophageal cancer was made. The Union for International Cancer Control stage of the disease was T4N0. The pathological results showed moderately differentiated adenocarcinoma. In view of this condition, we decided to give CB-CIK cell infusion and adjuvant radiotherapy. This treatment was approved by the ethics committee of the 323 Hospital of Chinese People's Liberation Army, and the patient provided written informed consent prior to her enrolment. Safety study of CB-CIK cells was registered in http://www.clinicaltrials.gov/ Protocol Registration System (NCT01914263). We used the medical linear accelerator for 3-dimensional (3D) intensity-modulated radiotherapy (Elekta Oncology Systems, Shanghai, China). The radiation treatment prescription dose was as follows: 2.5 Gy/fraction, for a total of 20 times, up to a total dose of 50 Gy. During her hospitalization, because of abdominal pain and burning sensation in the stomach, she was unable to receive radiotherapy; only a total of 12 times radiotherapy was

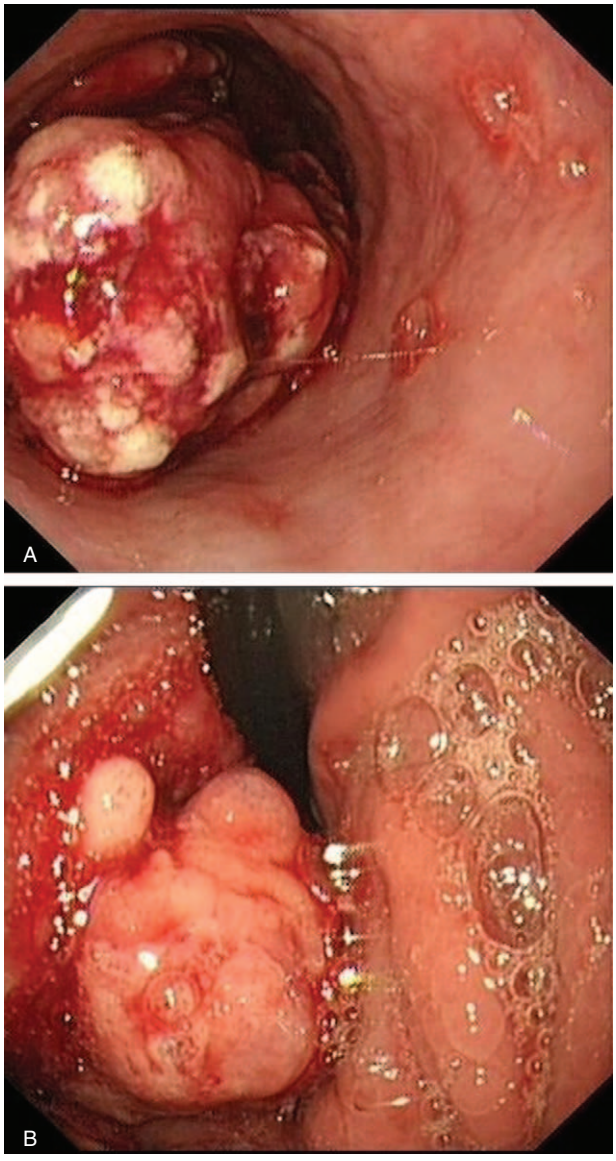

FIGURE 1. Electronic ultrasonic gastroscopy showed that (A) the middle esophagus was jammed with apophysis lesions and (B) esophageal tumor size was 2.5 ×2 cm involving the bottom of the stomach.

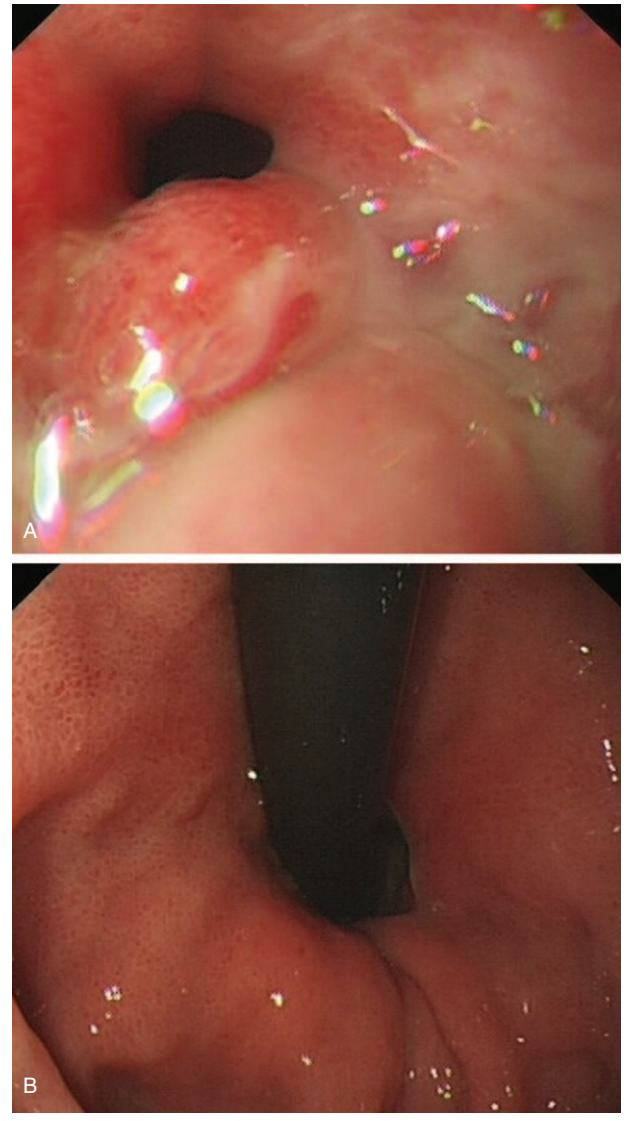

FIGURE 2. Electronic ultrasonic gastroscopy revealed that (A) the esophageal was unobstructed and (B) the tumor body had disappeared.

performed. Between the radiation intermittent periods, we made the umbilical cord blood CIK cells infuse back to the patient 6 times; each time the quantity of cell casting was 1×10^9/ 250 mL. After infusion, the patient had no symptoms such as fever, chills, nausea, and vomiting. Three days later we reviewed blood routine, urine routine, and liver and kidney function, and monitored the blood pressure, blood lipids, and blood glucose. They all had reached normal.

Second Treatment Procedures

Three months later, the second time in the hospital, the patient could eat semi-liquid diets, and her abdominal pain significantly reduced. According to the KPS, she scored 70 points; the biochemical analysis and electronic ultrasonic gastroscopy were performed. This time the patient completed 8 radiotherapies that were unfinished last time and was given CIK cell infusion 3 times. After this treatment, she was discharged from hospital.

Follow-Up and Outcomes

Three months later, the third time in hospital, the patient told that swallowing is obviously smooth. According to the KPS, she scored 90 points. The biochemical analysis and electronic ultrasonic gastroscopy were performed. A diagnosis of no apophysis lesion was made. The positron emission tomography/computed tomography (PET/CT) was performed. The patient was continued to be given CIK cell infusion 4 times. After CIK cell therapy, she was discharged from hospital. At follow-up, 1 year later, the patient's condition improved significantly well compared with the last time. The patient ate as

TABLE 1. Biochemical Data for the Patient

Parameters	Result			Reference Range
	Pretreatment	First Treatment	Second Treatment	
WBC (10^9 cells/L)	12.80	4.90	3.80	4.0–10.0
RBC (10^{12} cells/L)	3.45	3.93	3.95	3.50–5.50
HGB, g/L	105	122	128	110–150
PLT (10^9 cells/L)	404	170	214	100–300
CEA, ng/mL	4.98	5.62	4.26	<5
Fer, μg/L	184.2	106.10	159.8	12–150

CEA = carcino embryonic antigen, Fer = ferritin, HGB = hemoglobin, PLT = platelet count, RBC = red blood cell, WBC = white blood cell.

usual and was self-reliant. She had gained further weight and still survived until the last follow-up.

RESULTS

Before the treatment, biochemical analysis of the patient was performed, which showed carcino embryonic antigen was 4.98 ng/mL and ferritin was 184.2 ng/mL (reference range, 12–150 ng/mL) (Table 1). Electronic ultrasonic gastroscopy showed esophageal tumor size, which was 2.5 × 2 cm involving the bottom of the stomach; the middle esophagus was jammed with apophysis lesions (Figure 1A and B). Computed tomography showed esophagus thickening (Figure 2). A provisional diagnosis of esophageal cancer was made.

Three months later, the second treatment of biochemical analysis was performed, which showed that the carcino embryonic antigen was 5.62 ng/mL and ferritin was 106.10 ng/mL (reference range, 12–150 ng/mL) (Table 1). Electronic ultrasonic gastroscopy showed that necrosis had become fewer than before (Figure 3A) and esophageal tumor size had gradually reduced, which was about 2 × 1.5 cm (Figure 3B).

Three months later, the biochemical analysis was performed, which showed that the carcino embryonic antigen was 4.26 ng/mL and ferritin was 159.8 ng/mL (reference range, 12–150 ng/mL) (Table 1). Electronic ultrasonic gastroscopy revealed that the esophageal tumor was unobstructed and the tumor body had disappeared (Figure 4A and B). A diagnosis of no apophysis lesion was made. The PET/CT was performed, which demonstrated that the lower esophagus proximal to the heart became thick partially and the cardiac wall also became a bit thick, along with mild increased metabolism. It improved markedly comparable to that of last lesions. Although increased metabolism in lower esophagus remained mildly elevated, there was no sign of obvious tumor-specific performance and no tumor metastasis in the rest of the viscera tissue (Figure 5). The patient was continued to be given CIK cell infusion 4 times. After the CIK cell therapy, she was discharged from the hospital. At follow-up, 1 year later, the patient's condition improved significantly well compared with the last time. The patient ate as usual and was self-reliant. She had gained further weight and still survived until the last follow-up.

DISCUSSION

With the development of oncology and immunology in recent years, immunotherapy represents a novel path to obtain a durable and long-lasting response in cancer patients. CIK cells are activated T cells with natural killer properties that can be

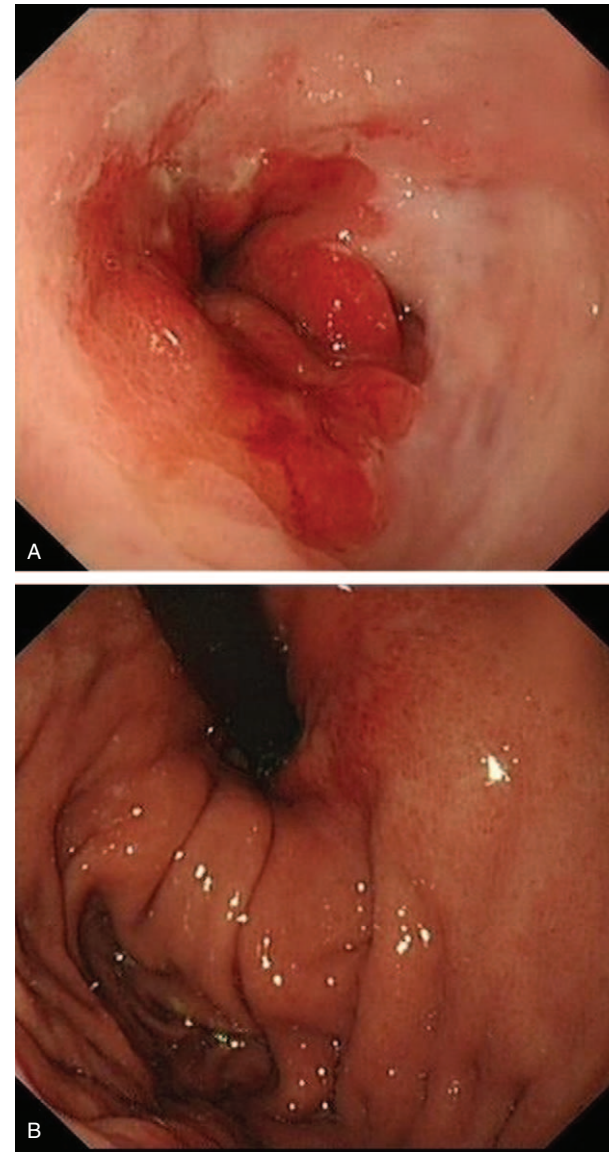

FIGURE 3. Electronic ultrasonic gastroscopy showed that (A) necrosis became fewer than before and (B) esophageal tumor size gradually reduced.

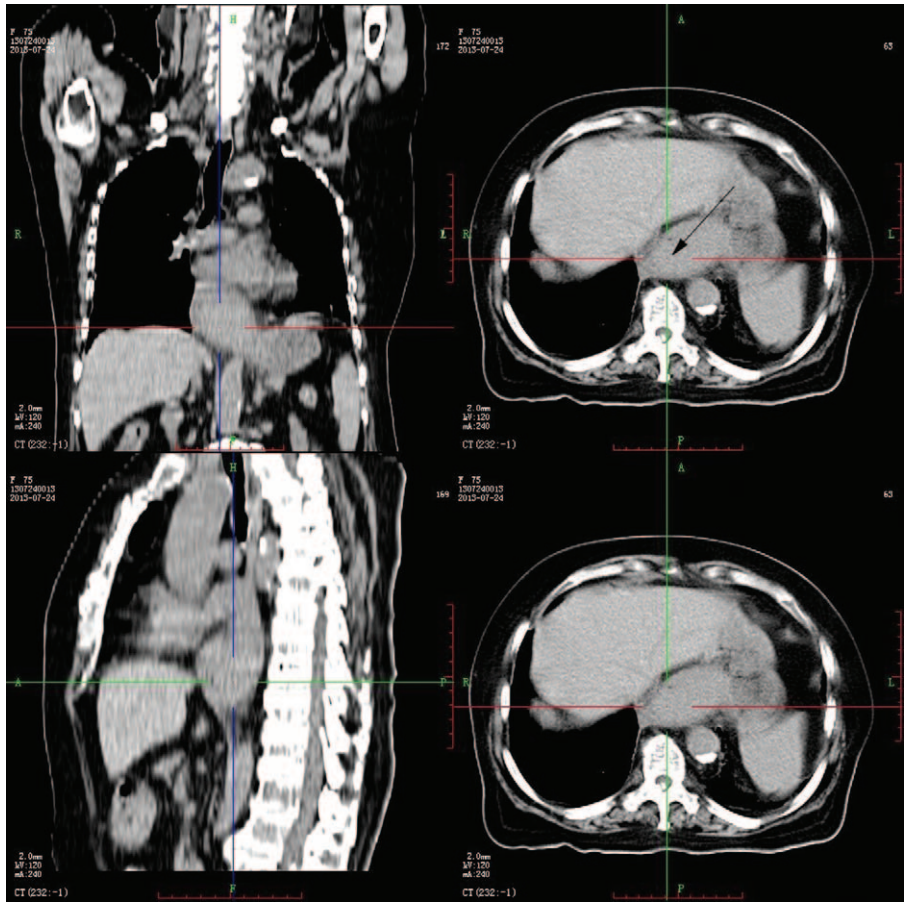

FIGURE 4. CT showed esophagus thickening (arrowed). Electronic ultrasonic gastroscopy revealed that (A) the esophageal was unobstructed and (B) the tumor body had disappeared. CT = computed tomography.

expanded in vitro in the presence of recombinant human interleukin-2 starting from peripheral blood mononuclear cells stimulated by interferon-γ and anti-CD3 antibody.[2] They are endowed with major histocompatibility complex-unrestricted antitumor activity. CIK cells are highly efficient cytotoxic effector cells capable of lysing tumor cell targets. Cultures of human CIK cells have been shown to have enhanced cytotoxicity and to proliferate more rapidly than lymphokine-activated killer cells by both in vitro and in vivo studies.[3] CIK cells express several chemokine receptors, and in vivo models suggest that they can migrate to the site of tumors after intravenous administration,[4–6] carrying out their cytotoxic potential and helping to control tumor growth.[7]

Medical linear accelerator for 3D intensity-modulated radiotherapy (Elekta Oncology Systems) can inhibit tumor cell proliferation to shrink tumors. Umbilical cord blood CIK cells can adjust the immune system, prompt the tumor cell apoptosis or kill tumor cells, and alleviate the adverse reaction of radiation. Thus, CIK cell therapy plus adjuvant radiotherapy can be a safe and effective treatment for esophageal cancer.

Umbilical CB-CIK cells are expanded from umbilical cord blood mononuclear cells by addition of a variety of cytokines in vitro culture, which are unlikely to produce cellular immune cross-reaction. In this case, during the treatment, the observed patient had no adverse reactions in umbilical cord blood CIK cell transfusion. After treatment, relevant biochemical indicators are normal: tumor markers significantly decreased and tumor gradually narrowed. Throughout the treatment, the patient had no pain and suffering with good tolerance; thus, it can improve the patient's quality of life and prolong the survival period of the patient with tumor.

In this case, the patient is old with esophageal cancer, not suitable for surgery and chemotherapy. In the light of our observations, we chose CIK cell immunotherapy plus radiotherapy for the patient. The treatment plan included the following radiation dose: single dose 2.5 Gy/fraction, for a total of 20 times, up to a total dose of 50 Gy, and umbilical cord blood CIK cell infusion was given 14 times. After treatment, the patient ate as usual and was self-reliant. She had gained further weight and appeared to be in good condition.

Recognition of this curative effect of sequent therapy for esophageal cancer is important to enable an appropriate treatment. This case highlights that the CIK cell therapy significantly alleviates the adverse reaction of radiation and improves the curative effect.

Autologous CIK cell infusion therapy for patients with malignancies is reported worldwide.[8–11] However, there are several drawbacks for autologous CIK limiting its clinical application. For example, limited cell numbers, decreased cell activities, and unavailable in time, and so on. Cord blood, as a novel source of nonsenescent lymphocytes for tumor immunotherapy, has been focused on recently. Our previous studies

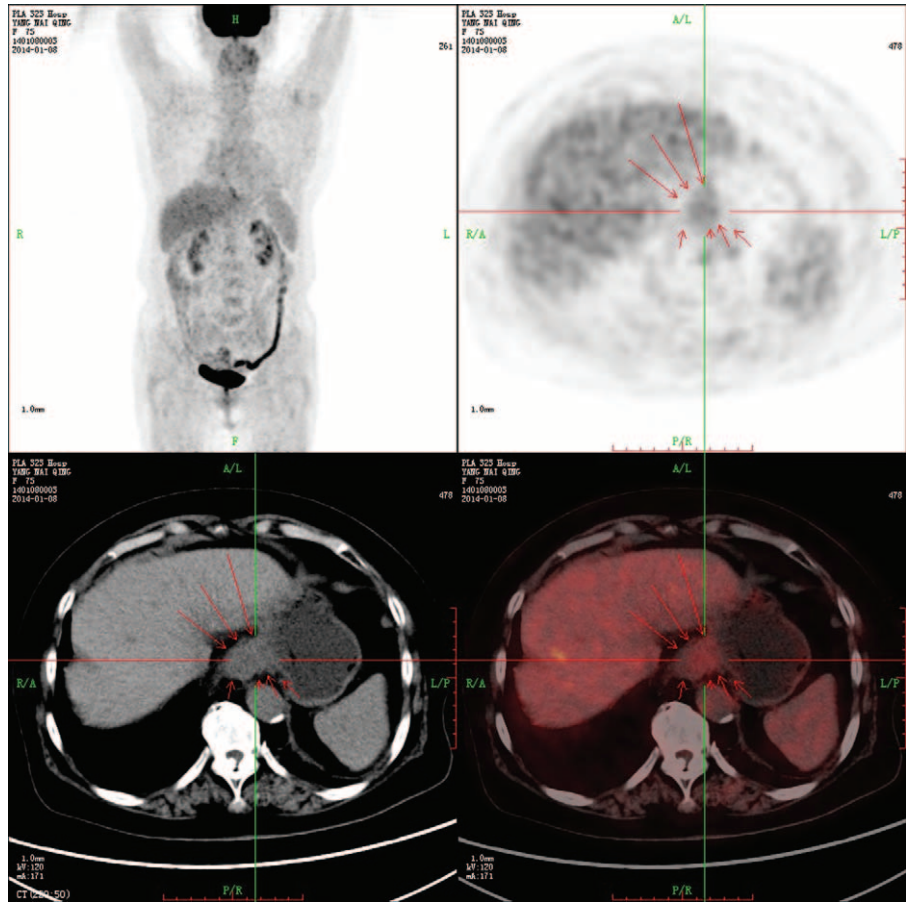

FIGURE 5. PET combined CT demonstrated that in spite of mild increased metabolism in lower esophagus, there was no sign of obvious tumor-specific performance and no tumor metastasis in the rest of the viscera tissue. CT = computed tomography, PET = positron emission tomography.

demonstrated that clinical scale expansion of CIK from cord blood is feasible.[12] Accumulating preclinical studies have shown that CB-CIK cells are potent antitumor effectors used in adoptive cancer immunotherapy. CIK cells represent a realistic new option in the field of cancer immunotherapy.[13]

CONCLUSION

This case highlights the advantage of umbilical cord blood CIK cell infusion in patients with esophageal tumor in intermittent radiotherapy. The mechanism for curative effect in this case was probably multifactorial. Medical linear accelerator for 3D intensity-modulated radiotherapy (Elekta Oncology Systems) can inhibit tumor cell proliferation to shrink tumors. Umbilical cord blood CIK cells can adjust the immune system, prompt the tumor cell apoptosis or kill tumor cells, and alleviate the adverse reaction of radiation. Thus, CIK cell therapy plus adjuvant radiotherapy can be a safe and effective treatment for esophageal cancer. It could improve a patient's quality of life and prolong the survival period of patients with esophageal tumor.

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