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Detection of the serum endothelin content in patients with acute lung injury and its value of severity evaluation

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ABSTRACT

Objective: To observe the correlation of serum endothelin content in patients with acute radiation lung injury and with the degree of inflammatory reaction and the lung functional level.

Methods: 68 Patients with non-small cell lung cancer who received the radiotherapy in treatment from May 2013 to October 2015 in our hospital were selected as the object of study. 25 patients who had acute radiation induced lung injury within 24 months of the radiotherapy were rolled in the radiation induced lung injury group (RILI group), and the rest of 43 without acute lung injury were rolled in the negative control group (NC group). The contents of endothelin, tumor necrosis factor α , interleukin-1 β , interleukin-6 in serum and the partial pressure of oxygen in artery, partial pressure of carbon dioxide in artery, vital capacity, forced expiratory volume in one second, maximal ventilatory volume, and diffusion capacity for carbon monoxide were tested.

Results: The content of serum endothelin of the patients in the RILI group [(69.3 \pm 7.5) pg/mL] were all obviously higher than that of the NC group [(24.1 \pm 2.9) pg/mL]; the content of the serum tumor necrosis factor α [(49.6 \pm 5.1) ng/mL vs. (22.7 \pm 3.1) ng/mL], interleukin-1 β [(29.4 \pm 3.3) ng/mL vs. (15.7 \pm 1.8) ng/mL], interleukin-6 [(163.4 \pm 20.3) pg/mL vs. (89.4 \pm 10.2) pg/mL] and the partial pressure of carbon dioxide in artery [(49.2 \pm 5.2) mmHg vs. (40.3 \pm 4.8) mmHg] were all obviously higher than that of the NC group, which were positively correlated with the serum endothelin content. But the partial pressure of oxygen in artery [(68.4 \pm 7.8) mmHg vs. (87.3 \pm 9.5) mmHg], vital capacity [(1203.4 \pm 136.5) mL vs. (2034.8 \pm 238.5) mL], forced expiratory volume in one second [(38.4 \pm 4.1)% vs. (58.3 \pm 6.2)%], maximum minute ventilation [(33.7 \pm 3.8) L/min vs. (66.1 \pm 7.9) L/min] and diffusing capacity of the lungs for carbon monoxide [(79.3 \pm 8.9)% vs. (86.7 \pm 9.4)%] were obviously lower than that of the NC group, which were negatively correlated with the serum endothelin content.

Conclusion: The elevated content of the endothelin in the serum of patients with acute radiation induced lung injury could assess the degree of inflammatory reaction and the lung functional level.

1. Introduction

Lung cancer is the malignant tumor in the first place of its occurrence rate and death rate in the world at present. Over 90% of the type of lung cancer is non-small cell lung cancer. For the past few years, with the continuous development of the radiotherapy technique, radiotherapy had become the most important way for the treatment of the non-small cell lung cancer, which could put off the growth of the tumor and lengthen the patients' life time^[1–3]. However, it will cause the damage of the normal lung tissues when the lung cancer cells are killed by the radiotherapy, and lead to the clinical symptoms, such as

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The study protocol was performed according to the Helsinki declaration and approved by the Ethics Committee of the hospital. The patients who were rolled in the groups had obtained informed consent.

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radiation induced lung injury cough, fever, dyspnea, and decline of lung function^[4–6]. The total occurrence rates are still over 15%, though the radiotherapy technique had been continually improved and the occurrence rate of the lung cancer had decreased^[7]. This disease essentially belongs to the aseptic inflammation and is difficult to get completely reversed and cure. To find out the disease and accurately evaluate and treat it at early stage would be conducive to improve the prognosis of patients^[8,9]. Some studies had reported that there was close relations between the acute radiation induced lung injury and the changes in serum endothelin content^[10,11], but the change conditions of the endothelin content in serum of the patients with acute radiation induced lung injury hadn't been reported. In the present study, the detection of the serum endothelin content in patients with acute lung injury and its value of severity evaluation of acute lung injury were analyzed.

2. Materials and methods

2.1. Cases materials

68 Patients with non-small cell lung cancer who received the radiotherapy in treatment from May 2013 to October 2015 in our hospital and were conformed to the following inclusion and exclusion criteria were selected as the objects of study. The inclusion criteria: the patients in the period of TNM III with ages of 30–70, who couldn't receive surgery, and expected life time of over 6 months, with normal lung function, more than 50% vital capacity in one second, normal hepatorenal function and bone marrow hematopoietic function, and no other coexisting malignant tumors and distant metastasis in lung cancer were found. The exclusion criteria: the patients with functional injury of liver and kidney, who had chronic complications of diabetes, coronary heart disease *etc.* were excluded from the study. This study was approved by the Ethics Committee of the hospital, and the patients who were rolled in the groups had obtained informed consent.

In the process of the radiotherapy, the following criterion was used to judge the occurrence of acute radioactive lung injury: the clinical symptoms are cough, fever and dyspnea, and through chest CT scanning, the homogeneous density flake-like obscured shadow and its border inside the lung lobes were found in accord with that in the radiotherapy; the symptoms still exist after one week regular treatment of the antibiotics, that were diagnosed to be the acute radiation induced lung injury after excluded pulmonary infection. The endpoint of observation was that the time of the occurrence of the acute radiation induced lung injury or 24 weeks after the radiotherapy, the patients with acute radiation induced lung injury were rolled in the radiation induced lung injury group (RILI group), and the other patients were rolled in the negative group (NC group).

2.2. Experimental method

The clinical index of patients in the RILI group was tested after the corresponding clinical symptoms of the lung injury appeared, and the clinical index of the patients in the NC group was tested after 24 weeks of the radiotherapy. 5–10 mL of the peripheral venous blood samples of patients in the two groups were collected at corresponding time, and serum samples were obtained by centrifugal separation after holding

under the indoor temperature condition, then the enzyme-linked immunosorbent assay kits (produced by Shanghai Westang Bio-tech CO., Ltd.) were used to test the contents of endothelin, tumor necrosis factor α , interleukin-1 β , interleukin-6; 2–5 mL of the peripheral venous blood samples were collected to tested the partial pressure of oxygen in artery (PaO₂) and partial pressure of carbon dioxide in artery (PaCO₂) by the blood gas analyzer, and the volume of forced expiratory volume in one second (FEV1), maximum minute ventilation (MVV), and diffusing capacity of the lungs for carbon monoxide (DLCO).

2.3. Statistical analysis

The software of SPSS19.0 version was used to enter and analyze the data. The measurement data were expressed as mean \pm SD and analyzed by *t*-test; the enumeration data were expressed by frequency form and analyzed by *Chi*-square test; the correlations between the above two variables were tested by Pearson's correlation analysis. *P* < 0.05 was regarded as the criterion that the differences were statistically significant.

3. Results

3.1. General materials of cases

25 Patients with occurrence of acute radiation induced lung injury in the 68 cases were rolled in the RILI group, which included 19 males and 6 females, whose ages were (38 \pm 4) years, BMI indexes were (22.5 \pm 2.6) kg/m², and the contents of ALT were (14.6 \pm 1.7) IU/L, AST were (17.1 \pm 1.5) IU/L, SCr were (68.3 \pm 7.2) μ mol/L, and BUN were (3.8 \pm 0.5) mmol/L before the treatment; The 43 patients who hadn't got the acute radiation induced lung injury within 24 weeks of the radiotherapy were rolled in the NC group, which included 33 males and 10 females, whose ages were (36 \pm 4) years, BMI indexes were (21.8 \pm 2.3) kg/m², and the contents of ALT were (15.1 \pm 1.6) U/L, AST were (16.7 \pm 1.9) IU/L, SCr were (65.8 \pm 6.8) μ mol/L, and BUN were (3.6 \pm 0.4) mmol/L before the treatment. According to statistic analysis, the genders, ages, BMI indexes, and the contents of ALT, AST, Scr, BUN had no differences (Table 1).

Table 1

General materials of patients in RILI group and NC group.

General material	RILI group (n = 25)	NC group (n = 25)	P
Gender (M/F)	19/6	33/10	< 0.05
Ages (years)	38 \pm 4	36 \pm 4	< 0.05
BMI (kg/m ²)	22.5 \pm 2.6	21.8 \pm 2.3	< 0.05
ALT (IU/L)	14.6 \pm 1.7	15.1 \pm 1.6	< 0.05
AST (IU/L)	17.1 \pm 1.5	16.7 \pm 1.9	< 0.05
Scr (μ mol/L)	68.3 \pm 7.2	65.8 \pm 6.8	< 0.05
BUN (mmol/L)	3.8 \pm 0.5	3.6 \pm 0.4	< 0.05

3.2. Contents of serum endothelin and inflammatory factors

The content of serum endothelin of the patients in the RILI group [(69.3 \pm 7.5)] vs. (24.1 \pm 2.9) pg/mL were all obviously higher than that of the NC group; Similar to variation tendency

of the content of serum endothelin, the content of inflammatory factors TNF- α [(49.6 \pm 5.1) vs. (22.7 \pm 3.1) ng/mL], IL-1 β [(29.4 \pm 3.3) vs. (15.7 \pm 1.8) ng/mL] and IL-6 [(163.4 \pm 20.3) vs. (89.4 \pm 10.2) pg/mL] were all obviously higher than that of the NC group (Table 2).

Table 2

Contents of serum endothelin and inflammatory factors in RILI group and NC group.

Content	RILI group (n = 25)	NC group (n = 25)	P
ET (pg/mL)	69.3 \pm 7.5	24.1 \pm 2.9	< 0.05
TNF- α (ng/mL)	49.6 \pm 5.1	22.7 \pm 3.1	< 0.05
IL-1 β (ng/mL)	29.4 \pm 3.3	15.7 \pm 1.8	< 0.05
IL-6 (pg/mL)	163.4 \pm 20.3	89.4 \pm 10.2	< 0.05

3.3. Lung functional indexes

The index of blood gas analysis PaO₂ [(68.4 \pm 7.8) vs. (87.3 \pm 9.5) mmHg] of the patients in the RILI group was obviously higher than that of the NC group; the indexes of respiratory function VC [(1203.4 \pm 136.5) vs. (2034.8 \pm 238.5) mL], FEV1 [(38.4 \pm 4.1)% vs. (58.3 \pm 6.2)%], MVV [(33.7 \pm 3.8) vs. (66.1 \pm 7.9) L/min], DLCO [(79.3 \pm 8.9)% vs. (86.7 \pm 9.4)%] were obviously lower than that in the NC group (Table 3).

Table 3

Lung functional indexes in patients of RILI and NC groups.

Index	RILI group (n = 25)	NC group (n = 25)	P
PaO ₂ (mmHg)	68.4 \pm 7.8	87.3 \pm 9.5	< 0.05
PaCO ₂ (mmHg)	49.2 \pm 5.2	40.3 \pm 4.8	< 0.05
VC (mL)	1203.4 \pm 136.5	2034.8 \pm 238.5	< 0.05
FEV1 (%)	38.4 \pm 4.1	58.3 \pm 6.2	< 0.05
MVV (L/min)	33.7 \pm 3.8	66.1 \pm 7.9	< 0.05
DLCO (%)	79.3 \pm 8.9	86.7 \pm 9.4	< 0.05

3.4. The correlations of the content of serum endothelin and inflammatory factor, lung function

The Pearson's correlation analysis had showed that the content of serum endothelin were positively correlated with the contents of serum TNF- α , IL-1 β , IL-6 and PaCO₂, of which *r* were respectively 0.73, 0.69, 0.66, 0.80, *P* < 0.05; And which were positively correlated with the contents of the PaO₂, VC, FEV1, MVV and DLCO, *r* were respectively -0.66, -0.79, -0.68, -0.72, -0.84, *P* < 0.05.

4. Discussion

In the above study, we analyzed the content of serum endothelin of patients with lung cancer radiotherapy in the time of occurrence of the acute radiation induced lung injury and found that it would lead to obvious rise of the content of serum endothelin. Endothelin, is polypeptide which consists of 21 amino acids, plays a role of inflammatory mediator in the acute and chronic airway diseases and lung diseases and participates in the processes of changes and development^[12–14]. The clinical study of Gu *et al.*^[15] has found that there was a close relation between the obviously elevated contents of serum endothelin

of the patients with acute radiation induced lung injury and respiratory distress syndrome and the recovery of the condition and the prognosis of disease. The animal experiment of Liu *et al.*^[16] has further confirmed that the content of serum endothelin in the rats with acute radiation induced lung injury was obviously elevated, and the expression of the endothelin in lung tissues was obviously up-regulation. There was not any report about the changes of the contents of serum endothelin of patients with acute radiation induced lung injury so far. This study has proved that the content of serum endothelin in the patients with acute radiation induced lung injury was obviously elevated, which showed that the elevated content of the serum endothelin was related to the occurrence of the acute radiation induced lung injury during the treatment of the radiotherapy.

Radiotherapy is the important approach for the treatment of non-small cell lung cancer, which could effectively kill the lung cancer cells and extend life time of the patients. However, the normal lung tissues would be injured when they were radiated to a certain degree, which causes a bad influence to the prognosis of the patients, and it was needed to intervene and prevent in the early stage^[4]. Radiation induced lung injury causes the symptoms of cough, fever, the decline of the lung function, and there would appear dyspnea and lung fibrosis with the progression of it, and even threaten the patients' life under severe condition^[17,18]. The occurrence of the radiation induced lung injury is related to the dose of partial radiotherapy, and radiotherapy dose is positively associated with partial control rate of the tumor, therefore, radiation induced lung injury is not only affected lung function and life of the patients, but also limited the cancer-killing effects of the radiotherapy^[6,19].

In recent years, radiation induced lung injury has been attracting more and more attentions. The pathologic nature of this disease is the aseptic inflammatory, which mediated by multiple cytokines, the inflammatory factors TNF- α , IL-1 β , IL-6 are penetrated in the whole process of the radiation induced lung injury^[20–22]. TNF- α , also called pro-inflammatory cytokine, is the cell activating factors with strongest biological activity, which is the key cytokines for the responses of mediate inflammatory^[23,24]; IL-1 β is the immune adjusting factor with extensive biological activities, which can adjust the synthesis, secretion and release of the different inflammatory mediators and has synergistic action in the inflammatory reaction^[25]. IL-6 is the central factor for activating and maintaining the inflammatory reaction, which can catalyze and enlarge the inflammatory reaction and is called the core factor that causes the damages of the tissues and the organs^[26]. After the analysis of the inflammatory factors in the serum of the patients with the acute radiation induced lung injury, we found that the content of the serum TNF- α , IL-1 β and IL-6 were positively correlated with the content of endothelin. And this shows that the inflammatory reaction mediated by TNF- α , IL-1 β and IL-6 has participated in the occurrence of the acute radiation induced lung injury, and the content of the serum endothelin is consistency with the content of the inflammatory factors, which can precisely assess the degree of the inflammatory reaction during the process of acute radiation induced lung injury. In the process of occurrence with acute radiation induced lung injury, the lung function has significant change with the expression of the relatively deficiency of ventilation and gas exchange functions^[27]. Our analysis results also show that the PaO₂, VC, FEV1, MVV and DLCO of the patients in RILI group are all lower than that of the NC group, which are negatively correlated with the

content of serum endothelin, but PaCO₂ is higher than that of the NC group and negatively correlated with the content of serum endothelin. These reveal that the patients with acute radiation induced lung injury have different injury degrees of the lung function, which express as the decline of the arterial oxygen content, the rising of the CO₂ content and the ventilation deficiency of airway. The content of the serum endothelin is consistency with the changes of lung function, and the change conditions of lung function can be accessed through a single index that can avoid the tedious process of lung functional examination.

In conclusion, lung function is obviously declined when the contents of the serum endothelin and inflammatory factor are obviously elevated. Moreover, the content of the endothelin in the serum of patients with acute radiation induced lung injury could assess the degree of inflammatory reaction and the lung functional level.

Conflict of interest statement

The authors report no conflict of interest.

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