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Serum Interleukin-27 Level in Different Clinical Stages of Lung Cancer

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Abstract

BACKGROUND: Advanced lung cancer is indicated with rapid disease development. Interleukin 27 (IL-27) is regarded as a cytokine with anti-tumour activities.

AIM: Since, the impact of type of lung cancer on the level of IL-27 in patient's serum has not yet been investigated; current study evaluated the clinical stages according to American Joint Committee on Cancer (AJCC) criteria, Tumor-Node-Metastasis (TNM) stage and the lung cancer spread (localized or widespread) and it's correlation with serum IL-27.

MATERIAL AND METHODS: Thirty patients with confirmed histopathological lung cancer and 30 cancer-free healthy individuals as the control group were included in the current study. Patients group were assigned to either small cell lung cancer group (SCLC) or non-small cell lung cancer (NSCLC) according to the clinical features and the results of lung biopsy specimens. Level of IL-27 was quantified with enzyme-linked immunosorbent assay (ELISA) test in serum samples.

RESULTS: A significant increase in serum IL-27 level was noticed in individuals with lung cancer in comparison with the control group. The level of serum IL-27 in the NSCL squamous carcinoma (NSCLC-Sc) type was significantly greater than in the NSCLC adenocarcinoma (NSCLC-Ad) type, and in both groups, this variable was more than the control group. The serum IL-27 content level was greater in stage III versus stage IV.

CONCLUSION: The current research confirmed the existence of the anti-tumour components in patients with NSCLC. IL-27 can be utilised in diagnosis and screening in early stages of lung cancer along with the management of patients. Different levels of IL-27 in different types of lung cancers in the current study can lead to design more comprehensive studies in the future.

Introduction

Cancer is still a global critical public health issue. Lung cancer is one of the most prevalent cancer types, leading to almost 18% of all cancer-related mortality across the world. Most patients show a poor prognosis. Therefore, diagnosis of a remarkable number of patients happens at advanced stages of the disease [1], [2]. In Iran, after car accidents and cardiovascular diseases, lung cancer is the third leading cause of death [3]. The aetiology of lung cancer remains inadequacy explained. The pathogenesis of lung cancer, however, is multifactorial. Lung cancer is divided into two main types: Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which is subdivided into NSCLC adenocarcinoma (NSCLC-Ad), NSCL squamous carcinoma (NSCLC-Sc), and NSCLC large cell carcinoma (NSCLC-LC) [4].

NSCLC accounts for nearly 80% of cases, with an overall 5-year survival rate of 13% [5], [6]. SCLC is an aggressive tumour that is known for it's

extensive and rapid metastatic dissemination and recurrence the following chemotherapy with a poor prognosis [7]. Surgery, chemotherapy and radiotherapy are the primary treatments for advanced NSCLC [8].

A definitive diagnosis is confirmed by tissue sampling that is often carried out by bronchoscopy [9]. Delay in diagnosis or treatment of lung cancer results in dissemination into the lung through metastasis. Early diagnosis of cancers, especially lung cancer, can significantly reduce mortality. Diagnosis of lung cancer is difficult in the early stages. Cell and chest mucus pathological tests, chest radiography (CTX) and CT-scan are some diagnostic methods for lung cancer. Non-invasive markers that are cost-effective and the new molecular and immunological diagnostic methods are crucial in the early stages of the disease [10].

Accumulating evidence shows that inflammation plays an important role in developing of the lung cancer, mainly in the induced cases by cigarette smoke and other noxious particles and gases [11], [12]. Immunoregulatory cytokines may play a fundamental role in tumour growth and metastases. The association of pro- and anti-inflammatory cytokines with histology type- or smoking-independent lung cancer risk has been demonstrated [13], [14]. Interleukin (IL)-27, which is a recently discovered member of the IL-12 family of cytokines, has been reported to exhibit anti-tumour activity in different preclinical test models because of anti-angiogenic, antiproliferative, and immune-enhancing effects [1], [15]. IL-27 is a heterodimer cytokine containing the Epstein-Barr virus-induced gene 3 (EBI3) and IL-27p28, which engages a receptor including gp130 and the IL-27Rα that activates activator of transcription (STAT) and Janus kinase (JAK)-signal transducer [16].

Few studies have been conducted to investigate the effect of IL-27 on lung cancers, with conflicting results, while most of them have been conducted on the mouse or in vitro and few of them have been conducted in vivo [17], [18], [19]. Given the importance of detecting lung cancer in the early stages and imprecision of some available diagnostic methods, it will be helpful to find a simple diagnostic procedure in which the serum is used.

In this regard, due to the non-toxicity of IL-27 in previous clinical studies and the discovery of its anticancer properties in other examined tumours [20], the present study investigated the use of IL-27 as an approach to the diagnosis of lung cancer. This study is also the first one to examine the association between IL-27 concentration and lung cancer according to the type of tumour. The concentration of IL-27 in various stages of lung tumour will also be investigated. The association between IL-27 in the circulatory system and lung cancer can be helpful in screening, evaluating and treating patients with pulmonary involvement symptoms.

Material and Methods

In this study, from September 2018 to September 2019, inclusion criteria were suffering from lung cancer with unknown causes and the age of over 18 years.

Definitive diagnosis of lung cancer for the referred patients was made based on clinical findings, the diagnosis made by an oncologist, and also histopathological examination on biopsy or tissue samples removed in lung surgery. Individuals with inflammatory or infectious diseases were excluded from the study. In the control group, individuals with a history of autoimmune or malignant disorders and those with a family history of lung cancer were not included in the study.

The sample size was calculated by using a cross-sectional study sample size calculation formula (Standard effect size = 1.1, α = 5%, β = 20%, and confidence interval = 95%). Then, 30 patients with lung cancer and 30 healthy non-cancer patients, as a control group [21], were selected by convenience sampling. The participants of the two groups were selected in a way that they were matched by age and sex.

The study protocol was confirmed at the Ethics Committee. After obtaining written consent to participate from the participants, demographic data were collected. Before treatment, 4 ml of complete venous blood samples of patients were collected in anticoagulant free tubes. In the laboratory, a serum sample was prepared and stored in a refrigerator at -20°C. The serum level of IL-27 of the samples isolated by enzyme-linked immunosorbent assay was evaluated using a kit (R & D Co.).

Patients, who were enrolled in the study, were diagnosed as either NSCLC or SCLC according to the results of their clinical specimens and a sample of lung biopsy. Clinical stages of patients were performed according to American Joint Committee on Cancer (AJCC) criteria, Tumor-Node-Metastasis (TNM) stage and the disease spread (localised or widespread) [22].

Data were statistically analysed by Statistical Package for Social Sciences (SPSS) (ver. 22.0; SPSS Inc. Chicago, IL, USA) software. Statistical analyses were conducted following international statistical standards. Continuous variables were expressed as mean ± standard deviation. Differences between two groups were analysed using the Mann – Whitney test for continuous variables. A p-value of < 0.05 was considered to be statistically significant.

Results

In this study, 30 patients with lung cancer were studied to investigate the relationship between cytokine IL-27 and lung cancer. 13 lung cancer patients had NSCL squamous carcinoma, and 11 had NSCLC adenocarcinoma (Figure 1).

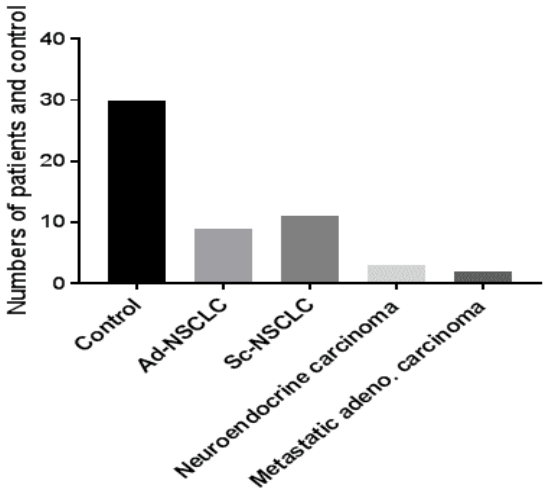

Figure 1: IL-27 values in lung cancer patients according to TNM classification. Bars express mean IL-27 value ± SD, pg/ml

An increase in serum IL-27 level was observed in patients with lung cancer in comparison with the control group with the Mann Whitney test. This study showed that the serum level of IL-27 in NSCLC-Sc type was higher than that in NSCLC-Ad type ($P < 0.05$). There was a significant difference between IL-27 level in control groups, NSCLC-Ad, and Sc-NSCLC ($P < 0.05$). There was also a significant difference between NSCLC-Ad group and NSCLC-Sc group ($P < 0.05$) regarding IL-27 level.

As illustrated in Figure 2, serum IL-27 levels are higher in the squamous cell carcinoma group than in the adenocarcinoma groups, and also are higher in both groups than in the control group.

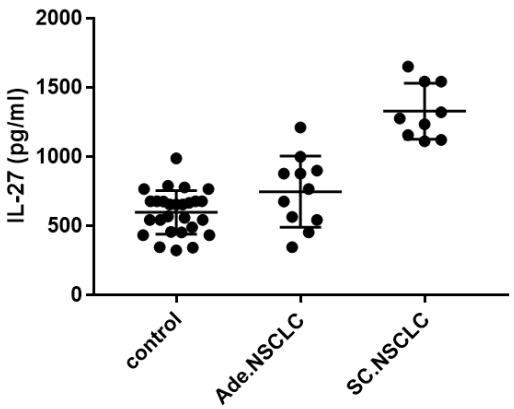

Figure 2: Serum level of Interleukin-27 in patients with lung cancer in comparison with the control group ($p < 0.05$, Mann-Whitney test)

In the next step, the IL-27 levels in the two groups were examined with the Mann-Whitney test according to different stages of the disease. Patients with III clinical stage showed a higher IL- 27 level in comparison with patients with clinical stage IV (Figure 3).

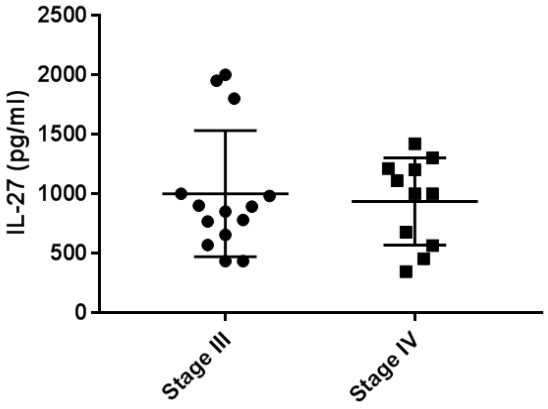

*Figure 3: IL-27 levels of lung cancer patients classified according to the AJCC. Values are expressed as mean ± SEM; *p < 0.05; **p < 0.01; c–controls*

Discussion

Several studies have recently suggested the role of IL-27 polymorphisms in the risk of developing different types of cancer such as nasopharyngeal carcinoma, hepatocellular carcinoma, oesophagal cancer, ovarian cancer, cervical cancer, and glioma with conflicting results [15], [23] but its role in lung cancer has not yet been studied. In this study, 30 patients with lung cancer and 30 healthy individuals participated. The primary aim of this study was to investigate the serum level of IL-27 in these two groups. The current study showed that the overall level of IL-27, irrespective of the type of cancer, was higher in patients with lung cancer than in the control group. NSCLC-Sc was the most frequent type of lung cancer among the samples. This type of lung cancer seems to have a higher prevalence in society so that in a study in China, most patients with NSCLC had squamous cell carcinoma (58.2%), and the rest were found to have adenocarcinoma (41.8%) [1], which is consistent with the present study.

It has recently been found that IL-27 produces strong antitumor effects against different tumour models through a variety of mechanisms in various cancer cell lines and in vitro, not only by exerting direct effects on the tumor cells but also by activating anti-tumor immune responses [20], including IL-27 antitumor, anti-inflammatory and antiangiogenic effects-mediated activities and activation of natural killer (NK) cells antimetastatic activities [21].

IL-27 antitumor components were also observed in lung cancer in another study. IL-27 seems to increase IFN-γ production that is necessary to differentiate TH0 to T-helper-1 (Th1) cells and induce cellular immune system [22].

Another aim of the present study was to investigate the level of IL-27 in various stages of lung cancer. In this regard, an increase in serum IL-27 level was observed in stage III of the disease compared to stage IV. This could indicate the importance of a tumour being concentrated in a part of the lung and metastasis has not been developed. In previous studies, it was also found that IL-27 will be very high if a pulmonary tumour is small and at the earlier stages [19].

Naumnik et al. did not observe any differences in IL-27 concentrations between patients with late-stage lung cancer and controls, and they also noted an insignificant increase in IL-27 in serum samples of patients of stage IIIB compared to those of stage IV [17]. Barrera et al. studied the association of cytokine profile with survival prognosis in serum samples of 110 NSCLC patients. Out of the investigated cytokines, IL-27 was significantly higher in non-smoker patients, the patients of IIIB stage, patients without CNS metastases, and those with positive pleural effusion [13], which is consistent with our study.

Karlicic et al. found that mean IL-27 concentration was significantly higher in healthy control people than in lung cancer patients and the severity of the disease dissemination was significantly correlated with IL-27 levels [19].

In the current study, IL-27 was indicated as a beneficial prognosis parameter in the early diagnosis of lung cancer. IL-27 was shown as a beneficial indicator in early diagnosis of lung cancer. Several previous studies have reported an increased level of serum IL-27 in association with several diseases, such as Sarcoidosis, allergic alveolitis and mainly pulmonary tuberculosis, which is also very life threatening and may result in death due to hemoptysis. Therefore, it is obligated to differentiate lung cancer from other diseases with similar manifestations. Tuberculosis and most of lung cancer types differ significantly in scientific signs, paramedical diagnostic strategies, direct sputum smear and the Ziehl–Neelsen stain, chest X-ray, CT [5], [7], [9], [10], [23].

Another aim of the study was to investigate the relationship between the level of IL-27 and the type of a lung tumour. To the best of our knowledge, this aim has not yet been taken into account in previous studies. In this study, examinations of serum samples and histopathology examinations of damaged tissues showed that the level of IL-27 was higher in Sc-NSCLC type than in NSCLC-Ad, which was not shown before. However, in contrast to the results of this study, Duan et al. observed a reduction of serum IL-27 concentration in NSCLC patients in comparison with the healthy controls [20]. The differences in the results can be due to the difference in the stage of cancer in the cited studies.

Also, the important findings of the current study and the higher levels of IL-27 in NSCLC-Sc than in NSCLC-Ad could be the reason for inconsistencies in the results of preceding studies, especially because the type of cancer was not addressed in past studies. Due to the role of lung cancer in serum IL-27 levels, discovered here, current study could be followed by greater comprehensive studies with larger sample size. However, a combination of different cytokines seems to play a role in the development of complex anti-inflammatory and anti-tumour properties in lung cancer and determine the prognosis of the disease.

In conclusion, the current study suggests that IL-27 can be used as an early diagnostic and screening tool for lung cancer. IL-27 seems to be a good indicator of for treatment response in lung cancer patients. In the current study, the differences in the level of IL-27 in different types of lung cancer was observed for the first time, which could be the basis for designing more comprehensive studies with larger sample sizes.

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