CLINICAL STUDY OF BASELINE CHARACTERISTICS AND GENE MUTATION SPECTRUM OF NON-SMALL-CELL LUNG CANCER PATIENTS WITH TUBERCULOSIS

Kewei Yu[1], Hongyu Qian[1], Zhiheng Xing[2], Haiying Peng[1], Bin Liu[1]
[1]Department of Respiratory and Critical Care Medicine, Tianjin Chest Hospital, Tianjin, 300000, China - [2]Medical Imaging Department, Tianjin Haihe Hospital, Tianjin, 300000, China

ABSTRACT

Objective*: To explore the baseline characteristics and gene mutation spectrum of non-small-cell lung cancer (NSCLC) patients with tuberculosis and provide more references for clinical diagnosis and treatment.*

Methods: *The clinical data of 102 NSCLC patients with tuberculosis admitted to our hospital from January 2015 to June 2020 were analyzed retrospectively. The baseline characteristics and gene mutation spectrum were analyzed to evaluate the correlation between the two.*

Results: *Among 102 patients, the proportion of males with smoking history was significantly higher than that of females (P<0.05). 54 patients received genetic testing, accounting for 52.94%. There was no significant difference between the whole population and those received genetic testing in terms of baseline characteristics (P<0.05). The percentage of active tuberculosis in patients with Stage IIIB-IV was significantly higher than that in patients with Stage I-IIIA (P<0.05). There was significant dif-ference between patients with and without cavity changes in the chest in histopathological type (P<0.05). The mutation rates of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) fusion, KRAS proto-oncogene (KRAS), ROS proto-oncogene 1,receptor tyro sine kinase (ROS1) and sarcoma viral oncogene homolog B1 (BRAF) were 35.90%, 4.00%, 10.00%, 3.70% and 4.55%, re-spectively; In NSCLC patients with tuberculosis, the gene mutation rate in females was significantly higher than that in males (P<0.05). The gene mutation rate of those without smoking history was significantly higher than those with smoking history (P<0.05). The gene mutation rate of those with adenocarcinoma was significantly higher than those without adenocarcinoma (P<0.05). The gene mutation rate of those with squamous carcinoma was significantly lower than those without squamous carcinoma (P<0.05). The gene mutation rate of those without cavity changes in the chest was signif-icantly higher than those with cavity changes in the chest (P<0.05). The mutation rate of EGFR of those without cavity changes in the chest was significantly higher than those with cavity changes in the chest (P<0.05).*

Conclusion: *NSCLC with tuberculosis has a high incidence in men who smoke for a long time, with adenocarcinoma as its main pathological type. At the same time, the gene mutation rates of NSCLC patients with tuberculosis are equivalent to those of NSCLC patients without tuberculosis. Patients with cavity changes in the chest have lower gene mutation rate.*

Keywords: *Tuberculosis, non-small-cell lung cancer, histopathology, gene mutation.*

DOI: 10.19193/0393-6384_2021_2_193

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Previous studies have showed that the incidence of lung cancer in people with tuberculosis can be 9-10 times as high as normal people, and the mortality risk of lung cancer patients with tuberculosis can also increase by 7-8 times[(1)]. In recent years, the precise treatment of lung cancer has come a long way, and new treatment techniques including targeted drugs and immune checkpoint inhibitors have been widely used in the treatment of lung cancer[(2, 3)]. However, there is still no clear conclusion on the treatment of lung cancer patients with tuberculosis, and it is still controversial whether more individualized treatment should be administered according to the characteristics of clinical data and laboratory examinations[(4)]. In this paper, the clinical data of 102 NSCLC patients

with tuberculosis ad-mitted to our hospital from January 2015 to June 2020 were analyzed retrospectively. Their baseline characteristics and gene mutation spectrum were analyzed, with a view to explore the baseline characteristics and gene mutation spec-trum of NSCLC patients with tuberculosis and provide more references for clinical diagnosis and treatment.

Data and methods

Object of study

102 NSCLC patients with tubercu-losis admitted to our hospital from Jan-uary 2015 to June 2020 were included in this study.

Inclusion criteria:

• NSCLC was confirmed by pleural effusion, needle biopsy of the lung or surgical histopath-ologic examination[5];

• Tuberculosis was confirmed simultaneous with or prior to the diagnosis of NSCLC[6];

• Age ≥18.

Exclusion criteria:

• The diagnosis of tuberculosis was later than that of NSCLC;

• Complicated by other malignant tumors;

• The clinical data were incomplete.

The study design complied with the Declaration of Helsinki, and the patients and their families signed informed consent.

Observed indicators

The demographic data, smoking history, tuberculosis status, clinical staging, histopathological examination, chest imaging and gene mutation testing of the patients were consulted. Among them, histopathological examination and genetic testing were done by the Department of Pathology of our hospital. The genetic testing was completed with the amplification-refractory mutation system (ARMS), and the kit was provided by Amoy Diagnostics Co. Ltd. (AmoyDx). The criteria for determining ALK fusion mutation was that both Ventana Im-munohistochemistry (IHC) and ARMS-polymerase chain reaction (PCR) were positive.

Statistical treatment

SPSS20.0 software was selected to process the data. The measurement data were compared by a t test and expressed as ($\bar{x}\pm s$).

The enumeration data were compared by a χ^2 test and expressed as %, with P<0.05 indicating statistically significant.

Results

Analysis of baseline characteristics

Among the 102 patients, there were 79 males and 23 females. 71 patients had smoking history, including 67 males and 4 females. The proportion of males with smoking history was significantly higher than that of females (P<0.05). 54 patients received genetic testing, accounting for 52.94%. There was no significant difference between the whole population and those received genetic testing in terms of baseline characteristics (P<0.05). See Table 1.

Among the 102 patients, there were 47, 40 and 15 patients in Stage I-IIIA, Stage IIIB-IV and undefined stage re-spectively. Among the patients in Stage I-IIIA, there were 7 and 40 patients with active tuberculosis and old tuberculosis respectively. Among the patients in Stage IIIB-IV, there were 11 and 3 patients with active tuberculosis and old tuberculosis respectively. The percentage of active tuberculosis in patients with Stage IIIB-IV was significantly higher than that in patients with Stage I-IIIA (P<0.05).

According to histopathological types, there were 51 cases with lung adenocarcinoma, 33 cases with lung squamous carcinoma, 10 cases with small cell lung cancer, 3 cases with adenosquamous carcinoma, 2 cases with neuroendocrine tumor, 2 cases with unclassified carcinoma and 1 case with large cell carcinoma. Among the 102 patients, 25 had cavity changes in the chest, including 12 cases with squamous carcinoma and 9 cases with adenocarcinoma, while 77 cases had no cavity changes in the chest, including 42 cases of adenocarcinoma and 22 cases of squamous carcinoma. There was significant difference between patients with and without cavity changes in the chest in histopathological type (P<0.05).

Indicator	Whole Population (n=102)	Patients Receiving Genetic Testing (n=54)	
Gender (case)			0.28
Male	78	39	
Female	23	15	
Age (yrs)	64.07±3. 89	63.62±3. 60	0.90
Smoking history (case)			0.49
Yes	71	36	
No	31	18	
Tuberculosis status (case)			0.55
Active	24	13	
Old	78	41	

Table 1: Analysis of baseline characteristics.

Analysis of gene mutation spectrum

Among the 102 cases, 54 received genetic testing, including 12 cases with squamous carcinoma and 42 cases without squamous carcinoma. Among them, the mutation rate of EGFR was 35.90% (14/39), including 42.86% (6/14) of exon 19 deletion, 50.00% (7/14) of exon 21 L858R mutation and 7.14% (1/14) of other mutations. The mutation rates of ALK, KRAS, ROS1 and BRAF were 4.00% (2/50), 10.00% (3/30), 3.70% (1/27) and 4.55% (1/22) respectively.

Analysis of the relationship between gene mutation and clinical characteristics

In NSCLC patients with tuberculo-sis, the gene mutation rate in females was significantly higher than that in males (P<0.05). The gene mutation rate of those without smoking history was significantly higher than those with smoking history (P<0.05). The gene mutation rate of those with adenocarcinoma was significantly higher than those without adenocarcinoma (P<0.05). See Table 2.

Indicator	With Gene Mutation (n=18)	Without Gene Mutation (n=36)	*P*
Gender (case)			0.00
Male	11	28	
Female	7	8	
Age (yrs)	63.59±3.70	64.10±4.01	0.93
Smoking history (case)			0.02
Yes	10	26	
No	8	10	
Tuberculosis status (case)			0.43
Active	4	10	
Old	14	26	
Tumor staging			0.11
I-IIIA	6	16	
IIIB-IV	11	17	
Undefined stage	1	3	
Histopathological type			
Adenocarcinoma	17	22	0.00
Non-adenocarcinoma	1	14	
Squamous carcinoma	1	13	0.00
Non-squamous carcinoma	17	23	
Cavity changes in the chest			
Yes	3	10	0.04
Squamous carcinoma	1	4	0.04
Non-squamous carcinoma	2	6	
No	16	26	0.00
Squamous carcinoma	1	8	
Non-squamous carcinoma	15	18	

Table 2: Analysis of the relationship between gene mutation and clinical characteristics.

In our study, 24 cases were complicated by cavity changes in the chest and received genetic testing. 3 of the 16 cases receiving EGFR genetic testing had mutation. The gene mutation rate of those without cavity changes in the chest was significantly higher than those with cavity changes in the chest (P<0.05). The mutation rate of EGFR of those without cavity changes in the chest was significantly higher than those with cavity changes in the chest (P<0.05). There was no significant difference between patients in Stage I-IIIA and Stage IIIB-IV in gene mutation rates (P<0.05). See Table 2.

Discussion

According to foreign studies, that tuberculosis infection can lead to an in-creased risk of lung cancer. 2-5 years after infection, the incidence of lung cancer was about 2-3 times that of normal people, and 5-12 years after infection, the risk was even higher[6, 7]. In addition, a retrospective cohort study evidenced that 20 years after infection, the incidence of lung cancer was still two times higher than that of normal people[8]. The proportion of males in the 102 lung cancer patients with tuberculosis included in this study was about 3.4 times that of females, which coincided with the previous reports, that is, the incidence rate in males was higher than that in females. An analysis of smoking history showed that about 85% of the males had smoking history, but the proportion of females was only 15%. Previous studies suggested that both tuberculosis and smoking were important risk factors for lung cancer, which can also explain why in our study, males had a higher incidence of NSCLC complicated by tuberculosis than females[9, 10].

This work indicated that patients in Stage IIIB~IV had a higher incidence of active tuberculosis than those in Stage I~IIIA. The possible reason for this phenomenon was that patients with advanced NSCLC had significantly reduced immune function and was more prone to active tuberculosis[11]. Most of the existing reports on histopathological types of lung cancer patients with tuberculosis posit that they should be dominated by squamous carcinoma. However, the main histopathological type of lung cancer in China is adenocarcinoma[12, 13]. The histopathological types of NSCLC patients with tuberculosis included in this study are principally adenocarcinoma (50%), and squamous carcinoma only accounted for 32%. The proportion of adenocarcinoma was especially high in patients without cavity changes in chest imaging. However, for those with cavity changes in the chest, squamous carcinoma became the main histopathological type (46%). In our study, 24 cases were complicated by cavity changes in the chest and received genetic testing. 2 of the 8 cases receiving

EGFR genetic testing had mutation. The gene mutation rates of those without cavity changes in the chest were significantly higher than those with cavity changes in the chest ($P<0.05$). The mutation rate of EGFR was only 16% in those with cavity changes in the chest, lower than those without cavity changes in the chest. The histopathological types of patients with cavity changes in the chest in our work were dominated by squamous carcinoma, which can explain the low mutation rate of EGFR in such patients to a certain extent. Among the 102 NSCLC patients with tuberculosis included in this study, 54 received genetic testing, including 12 cases with squamous carcinoma and 42 cases without squamous carcinoma. Therein, the mutation rate of EGFR was 35.90% (14/39), including 42.86% (6/14) of exon 19 deletion, 50.00% (7/14) of exon 21 L858R mutation and 7.14% (1/14) of other mutations. Existing studies hold that there are remarkable differences between Asian and European & American groups in EGFR mutation, and the mutation rate of EGFR in Asian group is above 40%, and higher in females than in males[14, 15]. On the other hand, our study also discovered that the mutation rates of EGFR in patients with smoking history and squamous carcinoma were 28% and 7.1% respectively, which were significantly lower than those without smoking history and adenocarcinoma. In addition, in keeping with the previous reports, there was no statistically significant difference in gene mutation rates between patients with active and old tuberculosis and between patients in Stage I-IIIA and Stage IIIB-IV[16].

There are still some shortcomings in our work: it is a single-center observational study, and the conclusion is subject to selection bias; the follow-up time is short, and the long-term survival benefits cannot be evaluated, which is yet to be confirmed in future studies. To sum up, NSCLC with tuberculo-sis has a high incidence in men who smoke for a long time, with adenocarcinoma as its main pathological type. At the same time, the gene mutation rates of NSCLC patients with tuberculosis are equivalent to those of NSCLC patients without tuberculosis. Patients with cavity changes in the chest have lower gene mutation rate.

References

1) Suliman AM, Bek SA, Elkhatim MS, et al. Tuberculosis following programmed cell death receptor-1 (PD-1) inhibitor in a patient with non-small cell lung cancer. Case report and literature review. Cancer Immunol Immunother, 2020, 7(10): 381-389.
2) Du D, Gu J, Chen X, et al. Integration of PET/CT Radiomics and Semantic Features for Differentiation between Active Tuberculosis and Lung Cancer. Mol Imaging Biol, 2020, 8(10): 733-740.
3) Zheng L, Yin J, Wang S, et al. Associated factors of co-existent tuberculosis and lung cancer: a case-control study. Eur J Clin Invest, 2020, 14(10): 2103-2111.
4) Miron O, Afrasanie VA, Paduraru MI, et al. The relationship between chronic lung diseases and lung cancer - a narrative review. J BUON, 2020, 25(4): 1687-1692.
5) He J. Clinical Oncology. Beijing: Peo-ple's Medical Publishing House, 2016: 43-44.
6) National Health and Family Planning Commission of China, Diagnostic Criteria for Tuberculosis (WS 288-2017). Electronic Journal of Emerging Infectious Diseases, 2018, 3(1): 59-61.
7) Tan KT, Kannan SK, Rajahram GS. A case of tuberculosis masquerading as lung carcinoma. Med J Malaysia, 2019, 74(6): 547-548.
8) Oh CM, Roh YH, Lim D, et al. Tubercu-losis is Associated with Elevated Risk of Lung cancer in Korea: The Nation-wide Cohort Study. J Cancer, 2020, 11(7): 1899-1906.
9) Borregón Rivilla M, Martínez Barroso K, Ramos Reguera I. Severe Pulmonary Parenchymal Involvement Due to Reactivation of Latent Tuberculosis in a Patient With Small Cell Lung Cancer. Arch Bronconeumol, 2020, 7(4): S0300.
10) Kim H, Kim HY, Goo JM, et al. Lung Cancer CT Screening and Lung-RADS in a Tuberculosis-endemic Country: The Korean Lung Cancer Screening Project (K-LUCAS). Radiology, 2020, 296(1): 181-188.
11) Ketai L. Tuberculosis and the Prospects for Lung Cancer Screening Worldwide. Radiology, 2020, 296(1): 189-190.
12) Honda Y. Lung Cancer and Respiratory Infections. Gan To Kagaku Ryoho, 2020, 47(5): 750-753.
13) Chan GH, Gwee YX, Low JL, et al. Immune checkpoint inhibition for non-small cell lung cancer in patients with tuberculosis or Hepatitis B: Experience from a single Asian centre. Lung Cancer, 2020, 146(8): 145-153.
14) Giller D, Giller B, Scherbakova G, et al. Extensive tracheal resection in lung cancer and tuberculosis: a case report. BMC Pulm Med, 2020, 20(1): 197-206.
15) Sun CY, Shen CI, Feng JY, et al. Severe hepatitis related to immune-checkpoint inhibitor in a patient with non-small-cell lung cancer and tuberculosis. Postgrad Med J, 2020, 20(8): 334-340.
16) Nanthanangkul S, Promthet S, Su-wanrungruang K, et al. Incidence rate of and Risk Factors for Tuberculosis among Cancer Patients in Endemic Area: A Regional Cohort Study. Asian Pac J Cancer Prev, 2020, 21(9): 2715-2721.

Corresponding Author:
Hongyu Qian
Department of Respiratory and Critical Care Medicine, Tianjin Chest Hospital, Tianjin, 300000, China
Email: hyqsci2021@163.com
(China)