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Original Research Article

Investigating Clinicopathological Characteristics and Mitotic Index [MI] in Patients with Neuroendocrine Tumor of the Lung

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ABSTRACT

Introduction: Most neuroendocrine tumor [NET] occurs in lungs, appendix, small intestine, rectum and pancreas. The main objective of this study was investigating clinicopathology in patients with neuroendocrine tumor of the lung.

Methods: In this present study we evaluated clinicopathological characteristics of 67 patients with lung neuroendocrine tumor referred to our center from 2016 to 2021

Results: The mean age was 56.62 years. Neuroendocrine tumors were more common in sixth decade [35.8%] of life. 76% were male and 23.9% were female. The most common types of neuroendocrine tumors were small cell lung cancer [SCLC], and typical carcinoid [TC] with frequencies of 56.3% and 23.4%, respectively. The frequency of large cell neuroendocrine carcinoma [LCNEC] and atypical carcinoid [AC] was 10.9% and 9.4%, respectively. So that typical carcinoid tumor was the most prevalent type in the fourth decade. However, SCLC and LCNEC tumors were more prevalent in the sixth decade, and 70% of atypical tumors were prevalent in patients under 40 years of age. TC, SCLC, and LCNEC tumors were more common in men compared to women. Besides, the average mitotic index in TC, AC, SCLC, and LCNEC tumors was 2.7%, 7.5%, 75.4%, and 54.16%, respectively.

Conclusion: Our data revealed the clinicopathological status of neuroendocrine tumor of the lung. So, paying attention to the clinical condition, age, gender of patients in this regard helps in timely diagnosis of this disease.

Keywords: Clinicopathology, Neuroendocrine Tumor, Lung.

Introduction

The incidence of neuroendocrine tumors of the lung has been increased in recent years. These tumors arise from enterochromaffin [EC] cells that normally present in the bronchial mucosa. These tumors represent a broad range of clinical and clinicopathological features. In 1991, Travis et al [1] proposed a new classification for neuroendocrine tumors of the lung, that include; typical carcinoid [low-grade malignancy], atypical carcinoid [intermediate-grade malignancy], and large cell neuroendocrine carcinoma [LCNEC] and small cell lung carcinoma [SCLC] [high-grade malignancy]. The prognosis and clinical characteristics of neuroendocrine tumors worsen according to the order mentioned [2]. These tumors account for more than 25% of all lung neoplasms, and the majority of neuroendocrine tumors are SCLC [3]. The treatment of these tumors highly depends on tumor histology features, which reflect differences in their clinical features and prognosis. The location of tumor and its biological invasion determine its clinical characteristics. In the cases of central carcinoids, recurrent infections, chest pain, cough, dyspnea, and pneumonia may occur. Cases with peripheral tumor are mainly among incidental findings. In contrast to high-grade NETs, carcinoid tumors develop in about 5% of patients with multiple endocrine neoplasia type 1 [MEN1] [4]. Well-differentiated neuroendocrine tumors [NETs] are capable of producing hormones similar to those of the nervous system. It's while, compared to gastrointestinal NETs, lung carcinoid tumors are rarely associated with a history of hypersecretion and paraneoplastic syndromes [5]. Carcinoid and Cushing's syndrome are mainly found in carcinoids and are rare only for patients with LCNEC or SCLC [6].

Jamati et al. conducted a study in 2016 aimed to investigate clinical and radiological symptoms and treatment methods for patients with carcinoid tumors. In this study, medical records of 21 patients with lung carcinoid tumors who referred to educational research and treatment center for tuberculosis and pulmonary diseases during the years 1374 to 1380 were investigated. In our study, out of 21 patients whose carcinoid tumor was definitely diagnosed through pathological tests, 19 patients had typical carcinoid tumor and 2 patients had atypical carcinoid tumor. Sex ratio was 1.1 with an average age of 39.33 years. Besides, the most common clinical symptom was cough [80.9%]. The tumors mostly located in the primary bronchus and the patients were treated by surgery with or without laser therapy. The most common surgical method used in treatment process of these patients was lobectomy [47.3%] [6]. Previous studies have shown that synaptophysin was more sensitive than Chromogranin A [CgA], especially in atypical carcinoid and SCLC.

Besides, TTF-1 together with Ki-67 index overexpression distinguishes SCLC from carcinoid [4]. Another study indicated that the diagnosis of LCNEC through preoperative biopsy or frozen section was the most difficult diagnostic procedure. T stage and pleural status are capable of predicting the outcome of SCLC and LCNEC [5].

In a study by Jafari et al [7], the co-occurrence rate of three markers of Ki67, Bcl2 and CD117 was investigated in two groups of SCLC and carcinoid tumor. Based on the findings of the present study, the co-occurrence of the aforementioned markers or the occurrence of BCL2/Ki-67 markers can be utilized in grading process of lung carcinoid tumor. Liu et al. [8] reported that the Ki-67 index test is an effective diagnostic marker for NET, which could distinguish AC and TC in 7% and, AC and LCNEC in 50% of cases.

LCNEC is biologically different from TC and AC, which has a more aggressive behavior and higher Ki-67 percentage score. At the present time, there is limited data about long-term clinical prognosis and prognostic and clinicopathological factors of lung carcinoid tumor. These tumors have complexities in terms of symptoms and clinical manifestations, stage and grade of malignancy, and markers such as Ki67. Considering the importance of the subject, the present study was conducted aimed to specify the clinicopathological characteristics of patients with lung NETs referred to the department of pathology of Shahid Sadoughi Hospital in Yazd during the years 2016-2021.

Materials and methods

The present study is a descriptive and analytic study that was performed based on a retrospective cross sectional studies approach during years 2016-2021. After obtaining the required permissions from the Department of Pathology and the Ethics Committee of Yazd University of Medical Sciences, the data about patients with lung carcinoid tumors lung who had referred to the department of pathology of Shahid Sadoughi Hospital in Yazd during the years 2016-2021 was recorded and investigated. Patient information, including age, gender, clinical manifestations, and Ki67 mitotic index, were extracted from the patient data and recorded. All affected patients were included in the study during this period, and the patients with incomplete records or unclear diagnosis were excluded from the study.

Data Collection Tools

At first, the proposal was approved by the research council of the pathology department and then the permission of the Ethics Committee of the Faculty of Medicine was obtained. After that, researcher

referred to the pathology department of Shahid Sadougi hospital in Yazd and collected the required data of patients using pathological documents through a pre-prepared checklist that includes age, sex, clinical manifestations, pathology diagnosis and Ki67 mitotic index

Sampling method and determining the sample size

Sampling was done based on convenience and availability of the patients. Through which the patients with lung NET who referred to the pathology department of Shahid Sadoughi Hospital in Yazd during the years 2015-2021 were included in the study through census.

Data analysis

After data collection, the data were analyzed using statistics such as Chi-Square and T-Test through SPSS Statistics V26. In all cases, a p-value less than 0.05 [typically ≤ 0.05] was considered as statistically significant.

Results

In the present study, 67 patients were examined whose average age was 56.62 years were evaluated. According to the findings of this study, NET was more prevalent among people in their sixth decade [35.8%] of life. The demographic characteristics of the patients participated in this study are presented in Table [1]. Table [2] indicates the frequency distribution of lung NETs. Besides, based on the data presented in Table [3], the average mitotic index [MI] in this study was 45.3%. The findings of this study regarding the frequency distribution of NET by gender revealed that TC, SCLC and LCNEC tumors were more common in men. On the other hand, nearly 70% of atypical tumors were observed in patients under the 40 years of old, and typical tumors were prevalent in the fourth decade. However, SCLC and LCNEC tumors were more prevalent in the sixth decade, so that the available difference in terms of happening years of tumors was significant. Comparison of frequency distribution of various types of NET based on Ki67 and MI is represented in Table 4.

The findings revealed that more than 50% of atypical and typical tumors had a low MI [less than 5%], while SCLC had an MI higher than 40% in 95.8% of cases. Comparing the average MI [Ki67] in all types of NET indicated that the average MI in TC, AC, SCLC and LCNEC tumors 2.7%, 7.5%, 75.4% and 54.16%, respectively [Table 5]. Here the most prevalent clinical symptoms were cough and dyspnea with a frequency of 35.8% and 29.9%, respectively.

Evaluating the frequency distribution of various types of NET based on the clinical symptoms presented in table [6] indicated that the clinical symptoms of patients with NET have no significant relationship with the types of tumors.

Table 1. Demographic characteristics of patients with lung NET

Variable	Frequency
Age [standard deviation \pm mean]	14.03 \pm 56.62
Less than 30 years	[4.5%] 3
30 to 40 years	[11.9%] 8
40 to 50 years	[10.4%] 7
50 to 60 years	[35.8%] 24
60 to 70 years	[17.9%] 12
More than 70 years	[19.4%] 13
Male to female ratio	51/16

Table 2. Frequency distribution of lung NET

Type of tumor	Frequency	Percentage [%]
Typical Carcinoid	15	22.5%
Atypical Carcinoid	6	9%
Small Cell Lung Carcinoma	36	53.7%
Large Cell Neuroendocrine Carcinoma	7	10.4%
Total	64	95.5%
Missing	3	4.5%
Total	67	100%

Table 3. Frequency distribution of MI [Ki67] in lung NETs

MI	Frequency	Percentage [%]
Less than 5%	16	23.9%
Between 5% - 25%	7	10.4%
Between 25% - 40%	2	3%
Over 40%	28	41.8%
Total	53	79.1%
Missing	14	20.9%
Total	67	100%

Table 4. Determination and comparison of frequency distribution of NET based on MI [Ki67]

Type of tumor	KI67 [%]				
	Less than 5%	5% - 25%	25% - 40%	Over 40%	Total
Typical Carcinoid	[92.9%] 13	[7.1%] 1	[0%] 0	[0%] 0	[100%] 14
Atypical Carcinoid	[50%] 3	[50%] 3	[0%] 0	[0%] 0	[100%] 6
Small Cell Lung Carcinoma	[0%] 0	[4.2%] 1	[0%] 0	[95.8%] 23	[100%] 24
Large Cell Neuroendocrine Carcinoma	[0%] 0	[16.7%] 1	[33.3%] 2	[50%] 3	[100%] 6
Total	[32%] 16	[12%] 6	[4%] 2	52	[100%] 50
P-value	0.001				

Table 5. Distribution and comparison of the average MI [Ki67] in all types of MET

Type of tumor	KI67 [%]	
	Average	Standard deviation
Typical Carcinoid	2.71	2.64
Atypical Carcinoid	7.5	4.32
Small Cell Lung Carcinoma	75.45	20.24
Large Cell Neuroendocrine Carcinoma	54.16	28.8

Table 6. Frequency distribution of various types of NET based on clinical symptoms

Type of tumor	Clinical symptoms				
	Cough	Dyspnea	Hemoptysis	Others	Total
Typical Carcinoid	[46.7%] 7	[20%] 3	[33.3%] 5	[0%] 0	[100%] 14
Atypical Carcinoid	[50%] 3	[16.7%] 1	[50%] 3	[0%] 0	[100%] 6
Small Cell Lung Carcinoma	[36.1%] 13	[38.9%] 14	[16.7%] 6	[36.1%] 13	[100%] 36
Large Cell Neuroendocrine Carcinoma	[0%] 0	[14.3%] 1	[14.3%] 1	[28.6%] 2	[100%] 7
Total	[35.9%] 23	[29.7%] 19	[23.4%] 15	[23.4%] 15	[100%] 64

Discussion

The factors such as sex, age, race, hereditary syndromes of multiple endocrine neoplasia type 1 [MEN1], family history, and smoking are among the risk factors of lung NET. Lung NETs account for 20-25% of lung cancers, which are distinguished from other lung tumors by their common morphological, immunohistochemical, and structural features. Lung NETs include typical carcinoid [a low-grade malignancy], atypical carcinoid [an intermediate-grade malignancy], and LCNEC and SCLC [as high-grade malignancies].

The results of this study revealed that the prevalence of NETs in the sixth decade [35.8%] of life is more common in men. The most common types of lung NETs in this study were SCLC and TC with incidence rates of 56.3% and 23.4%, respectively. The incidence rates of LCNES and AC was 10.9% and 9.4%, respectively. The findings of this study revealed that types of NETs have a significant association with age, gender and MI. So, typical tumor was more prevalent in the fourth decade of life, but SCLC and LCNEC tumors were more prevalent in the sixth decade of life, and 70% of atypical tumors were reported in patients less than 40 years.

TC, SCLC, and LCNEC tumors were more common in men compared to women, and the average MI in TC, AC, SCLC, and LCNEC tumors was 2.7%, 7.5%, 75.4%, and 54.16%, respectively. Besides, the MI of Ki67 in typical and atypical tumors was less than 5% and in SCLC and LCNEC tumors it was over 40%. The most common clinical symptoms of patients with lung NET were cough and dyspnea, respectively.

Jamaeti et al studied 21 cases of lung carcinoid tumors out of which 19 were typical carcinoid and 2 were atypical [6]. In their study the ratio of male to female was 1:1 with an average age of 39.3 years

old which is in line with the findings of our study.

In our study, the prevalence of lung carcinoids was also higher compared to SCLC and LCNEC tumors in the fourth decade. Based on the findings of the present study, the most common clinical manifestations of the patients were cough and dyspnea. Besides, in their study, the patients were treated through surgery with or without laser therapy, that is not assessed in the present study.

So, one of the main limitations of this study was the lack of examination of the treatments performed on the patients. In another study performed by Vahedi et al at Imam Khomeini Hospital, 27% of NETs were carcinoid tumors. In this study, the average age was also 49.6 years and the prevalence of these tumors was higher in men compared to women. The results of a study by Vahedi et al revealed that the difference of Ki67 value in patients based on their tumor grade, pathology type, tumor location and necrosis was significant. Their achievements are in line with the findings of our study in which various types of NETs were related to Ki67 percentage. In fact, using Ki67 marker can be helpful in diagnosing and determining the status of NETs, that guides making treatment decisions.

The percentage of Ki67 as a marker to determine the degree of malignancy and other characteristics related to the poor prognosis of NETs is in line with other studies such as Rindi et al. In his study Liu [8] indicated that the values of Ki67 marker for TC, AC and LCNEC tumors was 0-6.7, 9.9-25.7% and 63.2-91.9%, respectively which was in line with the results of the present study. Although, in their study the survival rate of patients with TC and AC did not differ, with the increment of tumor grade the survival rate of patients decreased, which is in line with other studies.

In contrast to our study, in their study the recurrence rate was also evaluated. Recurrence rate of LCNEC tumors was more compared to other tumors, so that all these tumors had recurrence, but no recurrence was observed in TC tumors. In their study in 2014, Travis et al. [1] indicated that the most important clinicopathological feature of lung NETs was Ki67 MI which can be effective in its differentiation. Their findings are in line with the results of the present study in this regard. Besides, the presence or absence of necrosis can be effective in its diagnosis. In his study, Zheng indicated that the Ki67 marker is less than 4-5% and 20-25% for TC and AC tumors, respectively. However, it is more than 40% and 50% for LCNEC and SCLC tumors, respectively. There is not necrosis in TC tumors, while focal necrosis is available in AC tumors as well as extensive necrosis in SCLC and LCNEC tumors.

Conclusion

The present study indicated that various types of NET have a significant relationship with age, gender and MI. Finally, it seems that paying attention to the characteristics of patients with lung NETs, including age, sex, clinical symptoms, and considering the MI of Ki67 and the degree of necrosis can be useful in diagnosing these patients.

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