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Brain Metastases, Large Cell Neuroendocrine Carcinomas and Prognosis

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Abstract

Objective: Pulmonary large cell neuroendocrine carcinomas (LNECs) are not common but brain metastases are common in LNEC patients. Because of their rarity, there are no randomized controlled trials on optimal treatment. Generally available data are based on case reports and retrospective studies. For this reason, we retrospectively analyzed patients with LNEC that we followed up for brain metastases to contribute to the literature.

Methods: Between 2009 and 2020, 38 patients with brain metastases diagnosed with LNEC in our center were reviewed retrospectively.

Results: 38 patients were evaluated. The mean survival time was 5.17 months (95% confidence interval (CI) : 3.17-7.13). In multivariate analysis showed us that; shorter overal survival is associated with age (p=0.001), uncontrol of primary cancer (p=0.014), presence of metachronous metastases (p=0.003), poor Eastern Cooperative Oncology Group (ECOG) performance score (p=0.025), and high uric acid level (p=0.001) and high lactate dehydrogenase (LDH) levels (p=0.009).

Conclusion: LNECs are rare but aggressive cancers. LNECs often metastasize to the brain. According to our study, high LDH, high uric acid, poor ECOG performance score, ≥65 years, metachronous metastasis, uncontrolled primary tumor are associated poor prognosis. LDH, uric acid, age, presence of metachron metastasis, controbility of primary tumor can be used as easy and inexpensive biomarkers to determine the prognosis and in the follow-up and treatment of patients with LNECs with brain metastases as metastases seen of other cancers.

Keywords: Brain metastasis,prognosis, lung cancer, large cell neuroendocrine carcinomas

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Beyin Metastazları, Büyük Hücreli Nöroendokrin Karsinomlar ve Prognoz

Öz

Giriş ve amaç: Pulmoner büyük hücreli nöroendokrin karsinomlar yaygın değildir, ancak büyük hücreli nöroendokrin krsinomlarda hastalarında beyin metastazları yaygındır. Nadir olmaları nedeniyle, optimal tedavi konusunda randomize kontrollü çalışma yoktur. Genel olarak mevcut veriler vaka raporlarına ve retrospektif çalışmalara dayanmaktadır. Bu nedenle literatüre katkı sağlamak amacıyla beyin metastazları nedeniyle takip ettiğimiz LNEC'li hastaları retrospektif olarak inceledik.

Yöntemler: 2009-2020 yılları arasında merkezimizde büyük hücreli nöroendokrin karsinom tanısı konulan beyin metastazı olan 38 hasta retrospektif olarak incelendi.

Bulgular: Otuz sekiz hasta değerlendirildi. Ortalama sağkalım süresi 5.17 (%95 güven aralığı (GA): 3.17-7.13) aydı. Çok değişkenli analizler bize şunu gösterdi; daha kısa genel sağkalım, yaş (p=0.001), primer kanserin kontrol edilememesi (p=0.014), metakron metastaz varlığı (p=0.003), düşük ECOG düşük performans skoru (p=0.025) ve yüksek ürik asit düzeyi (p=0,001) ve yüksek laktat dehidrogenaz (LDH) düzeyleri (p=0,009) ile ilşkili.

Sonuç: Büyük hücreli nöroendokrin karsinomlar nadir fakat agresif kanserlerdir. Büyül hücreli nörondokrin karsinomlar genellikle beyne metastaz yapar. Çalışmamıza göre yüksek LDH, yüksek ürik asit, kötü ECOG performans skoru, ≥65 yaş, metakron metastaz ve kontrolsüz primer tümör kötü prognoz ile ilişkilidir. LDH, ürik asit, yaş, metakron metastaz varlığı ve primer tümörün kontrol edilebilirliği, diğer metastazlar gibi beyin metastazı olan büyük hücreli nöroendokrin karsinomlu hastaların prognozunu belirlemede ve takip ve tedavisinde kolay ve ucuz biyobelirteçler olarak kullanılabilir. kanserler.

Anahtarkelimeler: Beyin metastazı, prognoz, Akciğer kanseri, büyük hücreli nöroendokrin karsinom.

INTRODUCTION

Neuroendocrine large cell carcinoma (LNEC) is extremely rare. LCNEC occurs in only 2-3% of all lung cancer cases[1,2]. But brain metastases are common in LNEC patients. LNECs are high grade, show aggressive course and poor prognosis. Brain metastases are also common in LNEC patients[2-6]. They have biologic and behavioural characteristics similar to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in clinical practice. Because they are rarely seen, it is not possible to conduct randomized clinical trials and, as a result, there is still no standardized approach for monitoring and treatment. The available information guiding the monitoring and treatment of patients is mostly retrospective information obtained by adapting the findings from SCLC and NSCLC to LNECs.

Considering the rare nature of these tumors and lack of randomized studies in this area, we aimed to contribute to the literature by retrospectively evaluating patients that were followed up in our center with a diagnosis of LNECs and developed brain metastases.

METHODS

We retrospectively analyzed 38 patients who were diagnosed with LNEC and developed brain metastases between 2009 and 2020. Characteristics of the patients such as sex, age, smoking habits, metastasis sites, blood albumin, uric acid, lactic dehydrogenase levels, hemoglobin, lymphocyte, white blood cell, neutrophil, and platelet values, whether the primary disease was under control, whether brain metastases were synchronous or metachronous, and survival time were recorded, and the relationship of survival with the remaining parameters was examined. Patients were grouped according Eastern Cooperative Oncology Group (ECOG) performance score (<3, ≥3) and age (<65 years and ≥65 years). Overal survival has been

defined as the time from diagnosis to death (for those that died) or the last follow-up (for the alive).

Statistical Analysis

Descriptive statistics were presented as numbers and percentages for categorical variables, and median with minimum and maximum values and mean ± standard deviation for numerical variables. Survival analysis was performed with the Kaplan-Meier method. Significant variables in the univariate analysis were introduced into a multivariate Cox model. p value <0.05 was considered significant in all statistical analyses.

RESULTS

In our study, 38 patients, 34 males (89.5%) and four females (10.5%) were analyzed. Patients had a mean age of 61.1 ± 8.48 years. Smoking habit was present in all patients. Two (5.25%) patients had solitary and 34 (94.75%) had multiple brain metastases. Brain metastases developed at the time of diagnosis in 22 (57.9%) patients and during the course of the disease in 16 (42.1%). Thirty-three (86.8%) patients presented with metastases in other organs in addition to the brain. Liver metastases were seen in 12 (31.6%) patients, adrenal metastases in 20 (52.6%), and bone metastases in 26 (68.4%) (Table I). The median uric acid value was 4.5 (2.5-11.5) mg/dL, and the median lactate dehydrogenase (LDH) value was 381 (129-9,800) U/L (Table II). The median overall survival was 5.17 (95% confidence interval: 3.17-7.13) months. The molecular test result was negative in nine (31%) patients and unknown in the remaining patients. In both the univariate and multivariate analysis, a significant relationship was observed between OS and age, poor ECOG performance score,uncontrol of primary cancer, presence of metachronous brain metastasis, high uric acid levels, and high LDH levels(Table III, figure 1).

Table I: Demographic and clinicopathological characteristics of the patients

Parameters		Number (n)	Percentage (%)
Age	<65 years	25	65.8
	≥65 years	13	34.2
Gender	Female	34	89.5
	Male	4	10.5
ECOG performance score	<3	29	76.3
	≥3	9	23.7
Metastasis site	Liver	12	31.6
	Bone	20	52.6
	Adrenal	26	68.4
Number of metastases	Single	2	5.25
	Two or more	36	94.75
Metastasis time	Synchronous	22	57.9
	Metachronous	16	42.1
Disease control outside the brain	In remission	25	65.8
	Not in remission	13	33.2
EGFR	Negative	9	31.0
	Unknow	29	69.0
ALK	Negative	9	31.0
	Unknow	29	69.0
BRAF	Negative	9	31.0
	Unknow	29	69.0

EGFR: epidermal growth factor receptor, ALK: anaplastic lymphoma kinase

Table II. Laboratory values of the patients

Parameters	Mean± SD/median (min-max)
Age	61.4 ± 8.48
Hemoglobin (g/dL)	12.43 ± 0.26
Albumin (g/dL)	3.5 ± 0.95
Uric acid (mg/dL)	4.5 (2.5-11.5)
Lactate dehydrogenase (U/L)	381 (129-9800)
Lymphocyte (/µL)	1.5 (0.5-3.2)
Neutrophil (/µL)	6.6 (2.5-9.8)
WBC (/µL)	9.2 (4.7-20.3)

SD: standard deviation, WBC: whole blood cell

Table III: Univariate and multivariate analyses of overall survival

	Univariate (HR, 95% CI)	p value	Multivariate (HR, 95% CI)	p value
Age (<65 vs ≥65)	2.17 (1.04-4.52)	0.04	1.84(1.16-2.92)	0.001
Gender	1.71 (0.59-4.97)	0.32		
ECOG (<3 vs 3≤)	2.56 (1.17-5.61)	0.019	1.60 (1.06-2.43)	0.025
Metastasis time (synchronous vs metachronous)	2.47 (1.13-5.41)	0.024	1.62 (1.05-2.53)	0.03
Disease control outside the brain	2.19 (1.04-4.59)	0.037	1.76 (1.12-2.76)	0.014
LDH	2.30(1.096-4.81)	0.028	1.85 (1.17-2.93)	0.009
Uric acid	1.59 (1.53-1.94)	0.002	1.94 (1.16-2.92)	0.001
Albumin	-0.48 (0.24-0.94)	0.033	1.07 (0.78-1.48)	0.78
Hemoglobin	-0.95 (0.76-1.20)	0.71		
Platelet	1.01 (0.99-1.004)	0.61		
Lymphocyte	1.00 (0.99-1.006)	0.69		
Neutrophil	1.01 (0.99-1.025)	0.26		
White blood cell	1.10 (0.83-1.45)	0.76		
Liver metastasis	0.069 (0.33-1.44)	0.32		
Bone metastasis	0.84 (0.41-1.68)	0.60		
Adrenal metastasis	0.86 (0.45-1.65)	0.60		

HR: hazard ratio, CI: confidence interval, ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase

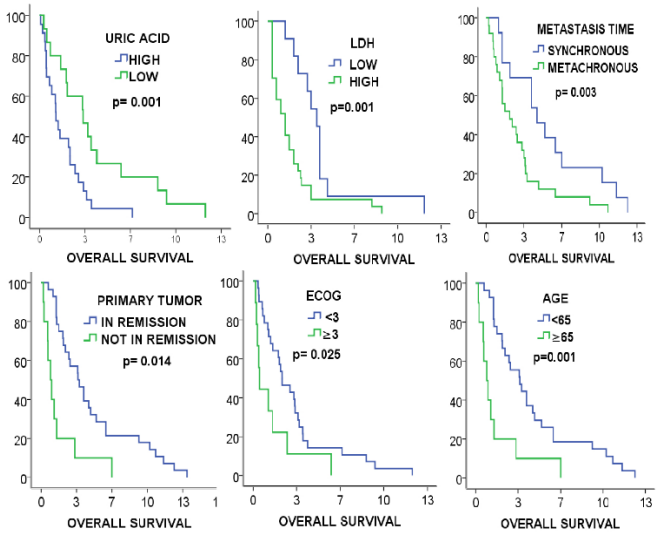

Figure 1: Kaplan-Meier curves show overall survival curves for lactate dehydrogenase curves (LDH), Age, Eastern Cooperative Oncology Group (ECOG) performance score, Primary tumor (in remission or not in remission,) and metastasis time (Synchronous or metachronous)

DISCUSSION

LNECS are rare but aggressive tumors. In the course of LNECs, brain metastasis is seen at a rate of 30%-50%[7-8]. LNECs, like SCLC, are high grade, have an aggressive course, show a poor prognosis and relapse frequently. Therefore the World Health Organization classified them as a neuroendocrine cancer of the lung similar to SCLC. However, they also share some clinical behavioral features with NSCLC.

In our study, 38 patients were enrolled. Patients had a mean age of 61.1 ± 8.48 years and the majority were men. Smoking habit was present in all patients. These findings are consistent with the literature and similar to the data reported for SCLC[1,8-10].

In contrast to SCLC that is centrally located, LNECs are peripherally located, and therefore they can remain asymptomatic for a long time in early stages and generally receive a diagnosis when symptoms and signs emerge in advanced stages. Distant metastases are also frequently encountered due to the diagnosis of LNECs in advanced stages. In the literature, it has been

reported liver, bone, and brain metastases are common in patients with LNECs[11]. Similarly, in our study, other organ metastases were observed in the patients with LNECs.

There are no randomized controlled studies on the follow-up and treatment of LNECs due to their rarity. Data are generally obtained from case reports with a small number of patients or retrospective studies. Since LNECs have some similar characteristics to SCLC and NSCLC, their follow-up and treatment are based on the adaptation of data obtained from these two. For example, as in NSCLC, in the early stages of LNECs, surgery is recommended for eligible patients[12,13-18]. Multimodal treatments are recommended for the treatment of locally advanced LNECs, and only chemotherapy (with SCLC-based treatment regimens) is recommended for the treatment of advanced LNECs[19-22]. In the literature, it has been reported that epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase-like (ALK) mutations may be positive in LNEC, similar to NSCLC. LNECs may benefit from treatments and immunotherapies targeting driver mutations, for example pembrolizumab, nivolumab and osimertinib[23-26]. But there is no data (study or case report) in the literature on targeted therapy with drugs targeting EGFR, ALK, BRAF, ROS-1 mutations and immunotherapies in LNEC patients with brain metastases.

Brain metastases are an indicator of poor prognosis in all cancers. According to the literature, brain metastases are seen between 19% and 47% in lung cancers[8,15]. Patients with LNEC with brain metastases have a shorter survival time. There is no standard treatment for LNEC patients with brain metastases as in other stages. Whole brain irradiation is recommended in patients who develop brain metastases, as in SCLC and NSCLC. However, with developments in radiotherapy techniques in recent years, there are studies suggesting that survival time may increase with stereotactic radiotherapy applied to selected patients[19,22]. As in SCLC, studies have also investigated efficacy of prophylactic brain radiotherapy in LNECs. However, the number of patients in these studies is small, and they report conflicting results; therefore, this treatment is not recommended as a standard[19].

The overall survival time of our patients and survival time after brain metastasis were similar to the literature. All the cases in our study, except for two, were multicentric. None of our patients was suitable for stereotactic radiotherapy.

Uric acid is the end product of nucleotide metabolism, which has both antioxidant and pro-oxidant properties. LDH, on the other hand, is a key enzyme in energy production, catalyzing the conversion of pyruvate to lactate in cancer cells. Therefore, the combination of uric acid and LDH can show tumor burden. In our study, we found a significant relationship between LDH, uric acid levels and median overall survival.

In earlier studies, LDH and uric acid level have been associated with many cancers[27].

However, the association between uric acid, LDH levels with prognosis has not been studied yet. Our study is the first to show the relationship between LDH, uric acid levels, and prognosis in LNECs, which are brain metastases.

In the literature, the ECOG performance score, age, number of brain metastases, presence of extracranial metastases, whether the primary cancer is under control, whether radiosurgery or surgery for brain metastases was found to be associated with prognosis in other solid cancers with brain metastases, and later studies developed scores based on these factors[28-30]. However, there is no prognostic data in the literature that includes only LNEC patients with brain brain metastases. We will need to polarize the data on prognosis in LNEC brain metastases

from studies on prognosis in other cancers as well as in the treatment of LNEC. For this reason, according to our study, if we compare the relationship between prognosis in patients with LNEC with brain metastases with the relationship between prognosis in other solid cancers with brain metastases, it is similar. In our study, according to the univariate and multivariate analyses, high LDH, high uric acid levels, poor ECOG performance score, ≥65 years, presence of metachron metastasis and uncontrol of primary cancers are associated with shorter OS. Therefore, these factors can be used in daily practice as prognostic indicators.

The limitations of our study are that the study was single-center, included a small number of patients, the number of patients undergoing molecular analysis was small, and it was retrospective. However our study is important because it is the first study to show prognosis and factors affecting prognosis in LNEC with brain metastasis.

In conclusion, LNECs are rare tumors but have an aggressive course, during which brain metastases frequently develop and significantly shorten the survival time of patients. Because they are so rare, there is no standardized follow-up and treatment for LNECs. According to our study, high LDH, high uric acid, poor ECOG performance score, age, metachronous metastasis, controllability of primary cancers can be used as easy and inexpensive biomarkers to determine the prognosis and in the follow-up and treatment of patients with LNECs with brain metastases as metastases seen of other cancers.

Ethical approval: Prior to the study, approval was obtained from the Health Sciences Ethics Committee of Manisa Celal Bayar University (decision number: 10.478.486, date: 05/02/2020).

Declaration of conflicting interests: The autors declare that they have no conflict of interest

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