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【 CASE REPORT 】

Large Cell Neuroendocrine Carcinoma of the Mediastinum Successfully Treated with Systemic Chemotherapy after Palliative Radiotherapy

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Abstract:
Large cell neuroendocrine carcinoma (LCNEC) is a highly malignant cancer originally found in lung in 1991. In extremely rare occasions, primary LCNEC is found in the mediastinum; approximately 40 of such cases have been reported. Due to the limited number of reported cases, a standardized treatment protocol has yet to be established. We report a case of a 66-year-old woman with primary mediastinal LCNEC who presented with superior vena cava syndrome. Emergent radiotherapy was performed, followed by systemic chemotherapy with cisplatin and etoposide, which resulted in a dramatic tumor reduction. This is the first report describing the achievement of a complete response after systemic chemotherapy in a patient with primary LCNEC.

Key words: large cell neuroendocrine carcinoma, LCNEC, mediastinum, thymus, superior vena cava syndrome

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a poorly differentiated neuroendocrine tumor arising from diffuse neuroendocrine systems. LCNEC was initially found in the lung (1); this was followed by several reports describing LCNEC in various organs, including the thymus, gastrointestinal tract and uterine cervix (2-4). Among these locations, primary LCNEC of the mediastinum is considered to be extremely uncommon; only around 40 cases have been reported. The majority of mediastinal LCNECs originate from the thymus, and thymic LCNECs have a poor prognosis in comparison to other types of thymic tumor due to the frequent occurrence distant and lymphatic metastasis, with a 10-year survival rate of 0% (5). Although a standard treatment approach has not been established, surgical resection remains the first choice. Systemic chemotherapy and radiotherapy are most often indicated as adjuvant therapy and their efficacy is yet to be proven. We herein report a case of primary mediastinal LCNEC of unknown origin. This is the first report to describe the achievement of a complete response (CR) in a patient with mediastinal LCNEC through systemic chemotherapy in conjunction with palliative radiotherapy.

Case Report

A 66-year-old woman with an 11-pack-year smoking history was admitted to our hospital for dyspnea, facial edema and dysphagia. On physical examination, both jugular veins were distended and the patient's face, neck and bilateral upper limbs were edematous. Blood tests revealed the following: neuron-specific enolase (NSE), 89.4 ng/mL; pro-gastrin releasing peptide (ProGRP), 1,930 pg/mL; and carcinoembryonic antigen (CEA), 4.4 ng/mL. Enhanced chest computed tomography (CT) revealed a solid mass of 106 mm in diameter in the anterior mediastinum that severely com-

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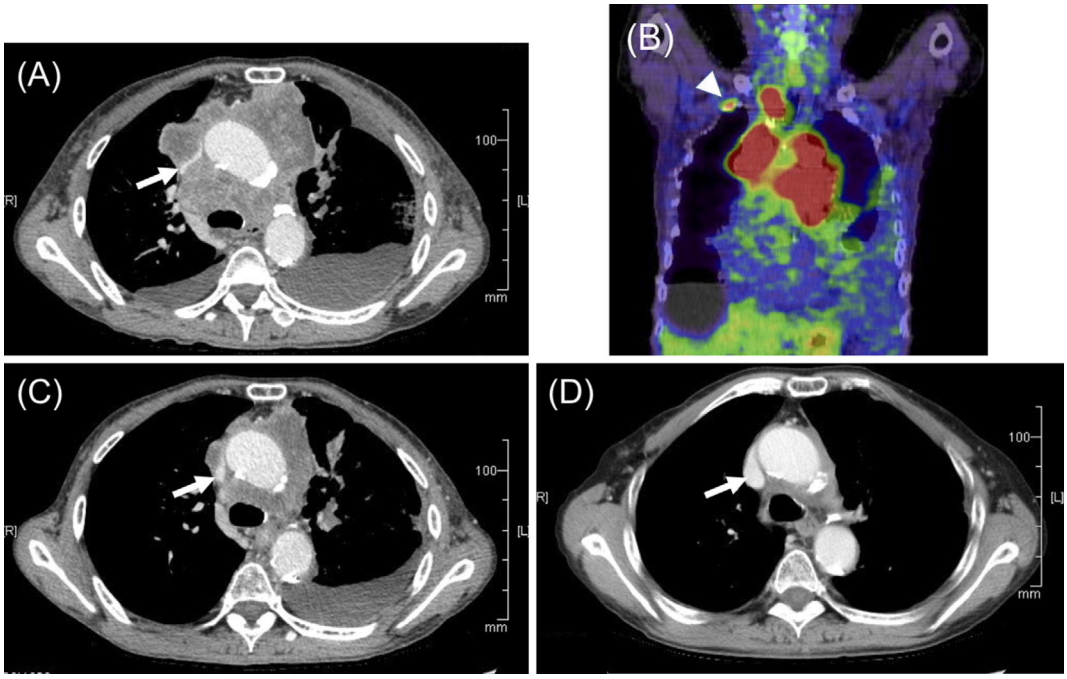

Figure 1. **(A) Enhanced chest CT revealed a solid mass of 106 mm in diameter with severe obstruction of SVC (arrow) in anterior mediastinum. (B) Intense uptake (SUV_{max}=16.9) of the tumor and right supraclavicular lymphnodes (arrowhead) without any other evidence of metastasis on PET/CT. (C) Patency of SVC was restored after radiotherapy. The tumor was reduced to 73 mm. (D) Chemotherapy with cisplatin and etoposide resulted in complete response of the tumor. SVC: superior vena cava**

pressed the superior vena cava (SVC) (Fig. 1A). positron emission tomography (PET)/CT revealed an intense uptake (SUV_{max} = 16.9) by the tumor and the right supraclavicular lymph nodes (Fig. 1B). No brain metastasis was found on enhanced brain CT. Immediately after CT-guided biopsy, palliative radiotherapy (total dose: 30 Gy/10fr) was initiated. The tumor was reduced in size to 73 mm in diameter and the SVC obstruction was partially resolved (Fig. 1C) with the improvement of the initial symptoms. A histological examination of the biopsy specimen demonstrated large pleomorphic cells with a high nuclear cytoplasmic ratio and vesicular chromatin, consisting of a solid tumor with large areas of necrosis (Fig. 2A and B). The average mitosis count was 33.3 mitoses per 2 mm^2. Immunohistochemistry was positive for neuroendocrine markers, including chromogranin A, synaptophysin, CD56 and Ki67 (Fig. 2C-F), and negative for thyroid transcription factor-1 (TTF-1). The Ki67 index was >50%. The high mitotic rate and immunohistochemical evidence of neuroendocrine markers were consistent with LCNEC (6).

Following palliative radiotherapy, the patient underwent systemic chemotherapy with four cycles of cisplatin (80 mg/m^2, on day 1) and etoposide (100 mg/m^2, on days 1, 2, and 3), which yielded a dramatic tumor reduction. On enhanced CT following chemotherapy, the tumor showed a CR (Fig. 1D); the CR has been maintained for six months.

Discussion

LCNEC is a high-grade tumor that is defined on the basis of histopathologic features of non-small cell cytology, positive staining for neuroendocrine markers, a high mitotic rate (>10 mitoses per 2 mm^2), and large areas of necrosis (6). Although LCNEC was initially recognized as a lung tumor (1), it has been observed in various organs.

The diagnosis of LCNEC is sometimes difficult, particularly in the case of small cell carcinoma or small cell-LCNEC combined-type, due to morphological continuum between LCNEC and small cell carcinoma. In the present case, as shown in Fig. 2, the tumor cells have all the features that differentiate them from small cell carcinoma: large cells with conspicuous nucleoli and more abundant cytoplasm in comparison to small cell carcinoma. Cell size is the most important diagnostic criterion to distinguish LCNEC from small cell carcinoma (7) and an arbitrary cut-off of three times the size of lymphocytes is usually used to distinguish “small” cells from “large” cells (6). As shown in Fig. 2A, the size of the tumor cells was obviously more than three times the size of a small resting lymphocyte. Small cell-LCNEC combined type, a subclass of small cell carcinoma, is defined as containing at least 10% large cells (6). Given the small size of the needle biopsy specimen and the heterogeneity of cancer cells, this type of small cell carcinoma would be possible. However, no small cells were

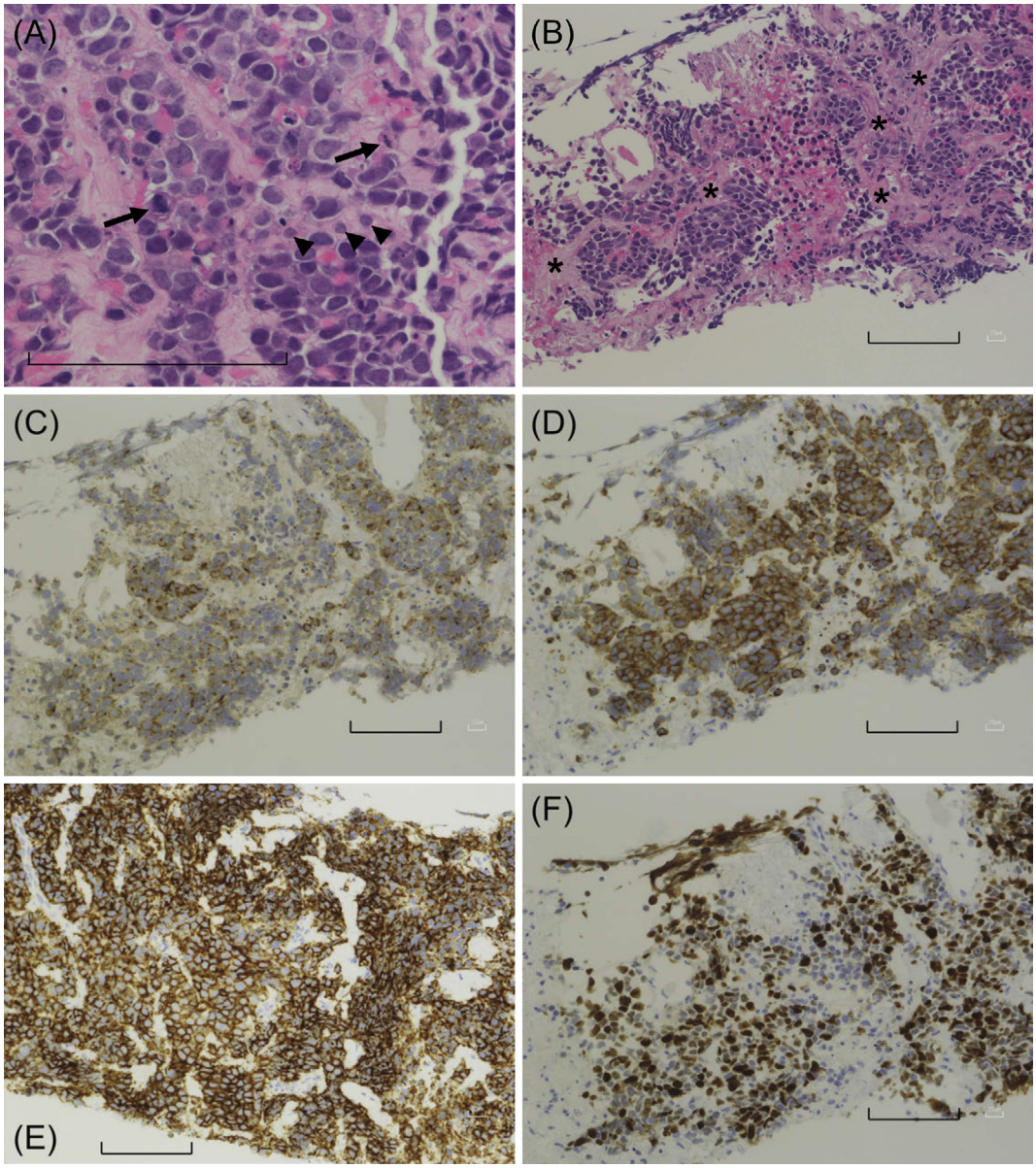

Figure 2. **Hematoxylin and Eosin (H&E) staining sections and immunohistochemistry of the tumor specimen. H&E staining reveals large pleomorphic cells with large nucleus and vesicular chromatin and high mitotic count (arrows) (A), consisting solid tumor with large areas of necrosis (asterisks) (B). Resting lymphocytes are also indicated (arrowheads) (A). Immunohistochemistry shows positive staining of chromogranin A (C), synaptophysin (D), CD56 (E) and Ki67 (D). Ki67 index was >50%. Scale bars: 100 μm.**

found in any of the needle biopsy specimen.

The tumor in the present case was presumably derived from the mediastinum because there was no pulmonary uptake on PET/CT. The current definition of LCNEC of the lung and thymus in the 2015 World Health Organization (WHO) classification (6) is based on the 2004 WHO classification. We searched the PubMed database (either English or Japanese papers) and the Japanese literature for all peer-reviewed case reports on mediastinal LCNEC published after the year of 2005. The prognosis was available for 36 cases, as shown in the Table (8-33). The origin, in the majority of the reported cases of mediastinal LCNEC, was the thymus. In the 2015 WHO classification for thymic neoplasms, LCNEC is categorized as one of four subclasses of thymic neuroendocrine tumor (6). Thymic neuroendocrine tumors are the least common thymic malignancy; they account for 2-5% of all thymic neoplasms. Among these, thymic LCNECs account for 14-26% of all thymic neuroendocrine tumors with an estimated incidence of 1 case per 20 million individuals (6). In the present case, since surgical resection was not performed and the thymus could not be identified on CT images, we were not able to determine whether the tumor originated from the thymus. There have been five previous reports on mediastinal LCNEC of unknown origin (Table).

LCNEC has a highly malignant nature and a high rate of

Table 1. Literature Review of Mediastinal Large Cell Neuroendocrine Carcinoma.

Case No.	Reference No.	Age	Sex	Origin	Chemotherapy	Radiotherapy	Surgery	Recurrence	RFS (months)	OS (months)	Survival status	
1	(8)	57	F	Thymus	Postop CBDCA + VP-16	Postop 50 Gy	Op	Yes	7	7	Alive	(ADF)
2	(9)	67	F	Thymus	Postop CDDP + VP-16	Postop 65 Gy	Op	Yes	6	9	Dead	
3	(10)	35	M	Unknown	Preop CDDP + VP-16 + BLM/ CDDP + PTX	None	Op	Yes	nd	12	Dead	(DOD)
4	(11)	44	M	Thymus	Postop Octoreotide	Postop Rx	Op	No	3	3	Alive	
5	(12)	48	M	Thymus	Preop Cx	Postop 51Gy	Op	No	73	73	Alive	
6	(12)	49	M	Thymus	Preop Cx	Postop 36Gy	Op	No	69	69	Alive	
7	(12)	50	F	Thymus	None	Postop 51Gy	Op	No	51	51	Dead	(DOD)
8	(12)	48	F	Thymus	None	Postop 60Gy	Op	No	13	13	Alive	(ADF)
9	(12)	46	M	Thymus	None	Postop 51 Gy	Op	No	95	95	Dead	(DOD)
10	(13)	46	M	Thymus	CDDP + CPT-11/ DTX + AMR	None	None	Yes	6	14	Dead	(DOD)
11	(14)	55	M	Thymus	Postop CDDP + CPT-11/ DTX + AMR	None	Op	No	16	16	Alive	(ADF)
12	(15)	44	M	Thymus	None	Postop 40 Gy	Op	Yes	7	13	Alive	
13	(16)	65	M	Unknown	CDDP + CPT-11	Whole brain radiation	None	Yes	0	11	Alive	
14	(17)	59	F	Thymus	None	Postop 50 Gy	Op	No	6	6	Alive	(ADF)
15	(18)	38	M	Thymus	Preop CDDP + ADM + VCR + CPA	Postop 50 Gy	Op	Yes	7	7	Alive	
16	(19)	42	M	Unknown	None	None	None	No	2	2	Dead	(DOD)
17	(20)	64	M	Thymus	Postop CDDP + ADM + CPA	Postop 45 Gy	Op	Yes	12	48	Alive	
18	(20)	57	M	Thymus	Preop CDDP + VP-16	Postop 60 Gy	Op	Yes	12	12	Alive	
19	(21)	67	M	Thymus	Postop Cx	Preop / Postop Rx	Op	Yes	3	3	Dead	(DOD)
20	(21)	42	M	Thymus	Preop Cx	Preop Rx	Op	Yes	1	7	Dead	(DOD)
21	(21)	72	F	Thymus	Preop Cx	Postop Rx	Op	Yes	2	4	Dead	(DOD)
22	(22)	65	F	Thymus	Postop PTX	None	Op	Yes	8	34	Dead	(DOD)
23	(23)	60	F	Thymus	None	None	Op	No	24	24	Alive	(ADF)
24	(24)	44	M	Thymus	Postop CDDP + VP-16	Preop 45 Gy	Op	No	36	36	Alive	(ADF)
25	(25)	53	M	Unknown	Preop CDDP + VRB	Preop 40 Gy	Op	Yes	7	9	Dead	
26	(26)	68	F	Thymus	Postop CDDP + VP-16	None	Op	No	17	17	Alive	(ADF)
27	(27)	71	F	Thymus	Postop CDDP + VP-16	None	Op	Yes	12	19	Alive	
28	(28)	51	F	Unknown	Preop CDDP + VRB	Preop 40 Gy / Postop 30 Gy	Op	No	15	15	Alive	(ADF)
29	(29)	75	F	Thymus	None	None	Op	No	57	57	Alive	(ADF)
30	(30)	28	F	Thymus	Postop CBDCA + PTX	None	Op	No	3	3	Alive	(ADF)
31	(31)	44	M	Thymus	nd	nd	nd	Yes	nd	36	Alive	
32	(32)	20	M	Thymus	Postop CDDP + VP-16	None	Op	No	9	9	Dead	(DOD)
33	(32)	39	M	Thymus	Postop CDDP + VP-16	None	Op	Yes	8	24	Alive	
34	(33)	80	F	Thymus	None	None	Op	Yes	nd	71	Alive	
35	(33)	57	F	Thymus	None	Postop Rx	Op	Yes	nd	30	Alive	
36	(33)	44	M	Thymus	Preop CDDP + VP-16	Preop Rx	Op	No	64	64	Alive	
37	Present case	66	F	Unknown	CDDP + VP-16	30 Gy	None	No	6	6	Alive	(ADF)

Preop: preoperation, Postop: postoperation, ADM: adriamycin, AMR: amrubicin, BLM: bleomycin, CBDCA: carboplatin, CDDP: cisplatin, CPA: cyclophosphamide, CPT-11: irinotecan, DTX: docetaxel, VCR: vincristine, PTX: paclitaxel, VCR: vincristine, VP-16: etoposide, VRB: vinorelbine, Cx: regimen not described, Rx: dose not described, Op: operative resection, RFS: recurrence free survival, OS: overall survival, ADF: alive diseae-free, DOD: dead of disease, nd: not described

recurrence. The overall survival (OS) and recurrence free survival (RFS) of the 37 cases listed in the Table are summarized in Fig. 3. Due to the obvious heterogeneity, the survival analysis of 37 patients will show a certain degree of imprecision; however, it still has some scientific merit because of the rarity of the disease. The median OS was 95 months [95% confidence interval (CI), 34 to not calculated] and the 5-year OS and the 10-year OS rates were 55.6 and 0%, respectively, which are consistent with the previously reported 5-year OS rates of 30-66% (9, 12, 34) and the pre-

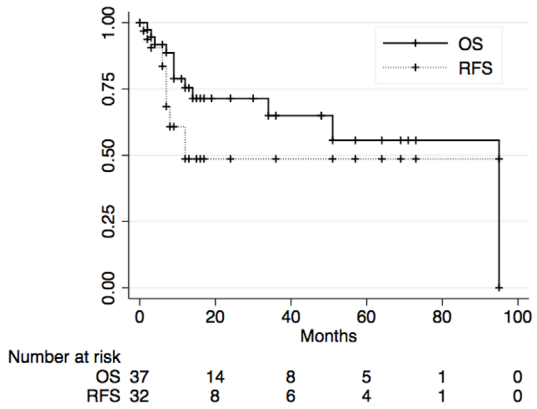

Figure 3. Overall survival (OS) and recurrence free survival (RFS) of mediastinal large cell neuroendocrine carcinomas listed in Table.

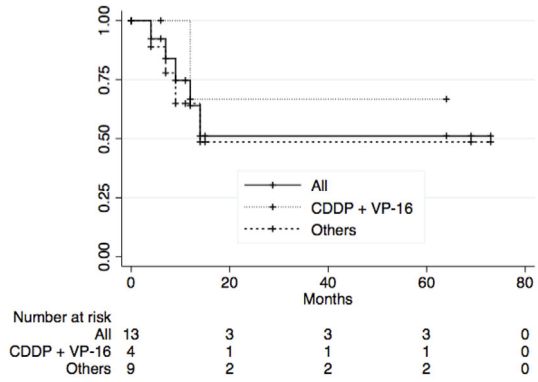

Figure 4. Overall survival (OS) stratified by chemotherapy regimen for 13 cases of mediastinal large cell neuroendocrine carcinomas initially treated with systemic chemotherapy listed in Table. The combination of cisplatin and etoposide ("CDDP+VP-16") is compared with other regimens ("Othres"). The OS of all 13 cases is also shown ("All").

viously reported 10-year OS rate of 0% (5). Recurrence was observed in 19 cases in the Table and the median RFS was 12 months (95% CI, 7 to not calculated). Distant metastasis was described in 13 cases; the sites included the lymph nodes, brain, lung, liver, spine, bone, and adrenal glands (9, 15, 16, 18, 20, 22, 25, 27, 31-33). We plan to closely follow the patient at bimonthly intervals to monitor locoregional and distant tumor recurrence.

The optimal therapeutic strategy for mediastinal LCNEC has yet to be established. The most salient feature of the present case is that a CR was achieved without surgical intervention. Among the 37 cases listed in the Table, only four cases were treated conservatively; among these cases, ours was the only case in which a CR was achieved. Surgery has been the mainstay of therapy for mediastinal LCNEC; however, data to support the efficacy of surgical resection are limited. The report of Gaur et al., which retrospectively analyzed 160 cases of thymic neuroendocrine tumor (35), was the only study to show that surgical treatment was significantly associated with favorable survival; however, the number of LCNECs was not documented.

SVC syndrome with central airway obstruction is potentially life-threatening and the patient received palliative radiotherapy shortly after CT-guided biopsy, which resulted in rapid tumor shrinkage, with a 31% reduction in diameter. As shown in the Table, radiotherapy was conducted as part of the initial treatment in 7 cases. The median reduction in tumor size in these cases ranged from 28% to 66%.

We proceeded with systemic chemotherapy after radiotherapy. In previous studies, the role of chemoradiotherapy was only described within the context of adjuvant or neoadjuvant therapy; no curative effect on untreated tumors has been reported. Although Nagata et al. reported that a CR was obtained with carboplatin and etoposide, which was used to treat distant relapse after complete resection (8), no other reports have described such a remarkable effect of systemic chemotherapy. Our case is, therefore, of great importance, in that it shows the potential for systemic chemotherapy to lead to a CR in primary mediastinal LCNEC. Since the standard chemotherapy regimen has not been established, data from lung LCNECs can provide some clues. For primary lung LCNEC, the efficacy of small cell lung carcinoma-based chemotherapy has recently been proven in two prospective studies (36, 37). Le Treut et al. reported that the median OS and progression-free survival of patients with advanced pulmonary LCNEC who were treated with cisplatin and etoposide were 8.0 months and 5.0 months, respectively (37). We selected these regimens based on the data and found a remarkable effect. There have been no systematic reports of the efficacy of different regimens for LCNEC of the mediastinum. In Fig. 4, we summarize the OS of 13 cases (from the Table) in which systemic chemotherapy was administered as an initial therapy. The combination of cisplatin and etoposide did not show a significant advantage in comparison to other regimens in this small cohort (p=0.59).

In conclusion, we reported a case of mediastinal LCNEC that was successfully treated with systemic chemotherapy. While surgery is thought to be the mainstay of therapy, our case shows that cisplatin and etoposide has the potential to produce a dramatic effect. This report suggests the possibility that systemic chemotherapy may play a curative role in the treatment of mediastinal LCNEC, a rare and intractable disease.

The authors state that they have no Conflict of Interest (COI).

References

1. Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol **15**: 529-553, 1991.

2. Ma J, Kimura W, Takeshita A, Hirai I, Moriya T, Mizutani M. Neuroendocrine carcinoma of the stomach with peripancreatic lymph node metastases successfully treated with pancreaticoduo-

denectomy. Hepatogastroenterology **54**: 1945-1950, 2007.
3. Selvakumar E, Rajendran S, Balachandar TG, et al. Neuroendocrine carcinoma of the ampulla of Vater: a clinicopathologic evaluation. Hepatobiliary Pancreat Dis Int **7**: 422-425, 2008.
4. Embry JR, Kelly MG, Post MD, Spillman MA. Large cell neuroendocrine carcinoma of the cervix: prognostic factors and survival advantage with platinum chemotherapy. Gynecol Oncol **120**: 444-448, 2011.
5. Cardillo G, Rea F, Lucchi M, et al. Primary neuroendocrine tumors of the thymus: a multicenter experience of 35 patients. Ann Thorac Surg **94**: 241-245, 2012.
6. Nicholson AG, Matsuno Y, Chan JKC, et al. Thymic neuroendocrine tumors. In: WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart. 4th ed. Travis W, Brambilla E, Burke A, Marx A, Nicholson A, Eds. IARC, Lyon, 2015: 234-243.
7. Marchevsky AM, Gal AA, Shah S, Koss MN. Morphometry confirms the presence of considerable nuclear size overlap between "small cells" and "large cells" in high-grade pulmonary neuroendocrine neoplasms. Am J Clin Pathol **116**: 466-472, 2001.
8. Nagata Y, Ohno K, Utsumi T, Sasaki Y, Suzuki Y. Large cell neuroendocrine thymic carcinoma coexisting within large WHO type AB thymoma. Jpn J Thorac Cardiovasc Surg **54**: 256-259, 2006.
9. Mega S, Oguri M, Kawasaki R, Hazama K, Iwai K, Kondo S. Large-cell neuroendocrine carcinoma in the thymus. Gen Thorac Cardiovasc Surg **56**: 566-569, 2008.
10. Takezawa K, Okamoto I, Fukuoka J, et al. Large cell neuroendocrine carcinoma of the mediastinum with α-fetoprotein production. J Thorac Oncol **3**: 187-189, 2008.
11. Dutta R, Kumar A, Jindal T, Mathur SR. Neuroendocrine carcinoma of the thymus gland with sternal invasion. Interact Cardiovasc Thorac Surg **8**: 694-696, 2009.
12. Cardillo G, Treggiari S, Paul MA, et al. Primary neuroendocrine tumours of the thymus: a clinicopathologic and prognostic study in 19 patients. Eur J Cardiothorac Surg **37**: 814-818, 2010.
13. Haga T, Nakajima Y, Kitamura A, Kuroda F, Takiguchi Y, Tatsumi K. A rare case of large cell neuroendocrine carcinoma of the thymus. Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc) **48**: 755-758, 2010 (in Japanese, Abstract in English).
14. Ogawa F, Iyoda A, Amano H, et al. Thymic large cell neuroendocrine carcinoma: report of a resected case-a case report. J Cardiothorac Surg **5**: 115, 2010.
15. Dutta R, Kumar A, Julka PK, et al. Thymic neuroendocrine tumour (carcinoid): clinicopathological features of four patients with different presentation. Interact Cardiovasc Thorac Surg **11**: 732-736, 2010.
16. Nojima D, Kiura K, Hotta K, Takigawa N, Tabata M, Tanimoto M. Large cell neuroendocrine carcinoma of the mediastinum. Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respir Soc) **48**: 506-510, 2010 (in Japanese, Abstract in English).
17. Ogawa H, Tanaka Y, Wakahara T, Tauchi S, Kazuya U, Yoshimura M. A resected case of large-cell neuroendocrine carcinoma in the thymus. Nihon Kokyūki Geka Gakkai Zasshi (J Jpn Assoc Chest Surg) **25**: 198-202, 2011 (in Japanese, Abstract in English).
18. Saito T, Kimoto M, Nakai S, et al. Ectopic ACTH syndrome associated with large cell neuroendocrine carcinoma of the thymus. Intern Med **50**: 1471-1475, 2011.
19. Lukina O, Gorbunkov S, Dvorakovskaja I, Varlamov V, Akopov A. Fast-growing large cell neuroendocrine carcinoma of mediastinum. Ann Thorac Surg **91**: 1618-1620, 2011.
20. Yoon YH, Kim JH, Kim KH, et al. Large cell neuroendocrine carcinoma of the thymus: a two-case report. Korean J Thorac Cardiovasc Surg **45**: 60-64, 2012.
21. Ahn S, Lee JJ, Ha SY, Sung CO, Kim J, Han J. Clinicopathological analysis of 21 thymic neuroendocrine tumors. Korean J Pathol **46**: 221-225, 2012.
22. Adachi H, Yamamoto T, Saito S, Rino Y, Masuda M. A case of poorly differentiated neuroendocrine carcinoma of the thymus. Nihon Kokyūki Geka Gakkai Zasshi (J Jpn Assoc Chest Surg) **26**: 203-207, 2012 (in Japanese, Abstract in English).
23. Machino R, Tagawa T, Yamasaki N, Miyazaki T, Hayashi T, Nagayasu T. Combined thymic epithelial tumor containing a component of large cell neuroendocrine carcinoma. Nihon Kokyūki Geka Gakkai Zasshi (J Jpn Assoc Chest Surg) **26**: 762-767, 2012 (in Japanese, Abstract in English).
24. Ose N, Inoue M, Morii E, Shintani Y, Sawabata N, Okumura M. Multimodality therapy for large cell neuroendocrine carcinoma of the thymus. Ann Thorac Surg **96**: e85-e87, 2013.
25. Maeda A, Nakata M, Yasuda K, et al. Unknown primary large cell neuroendocrine carcinoma (LCNEC) in the mediastinum. Gen Thorac Cardiovasc Surg **61**: 542-545, 2013.
26. Nishizawa N, Osaki T, Kanayama M, Nakagawa M, So T, Kodate M. A case of a large cell neuroendocrine carcinoma of the thymus. Haigan (Jpn J Lung Cancer) **55**: 1092-1097, 2015 (in Japanese, Abstract in English).
27. Takemoo T, Mizuuchi H, Sato K, Suda K, Iwasaki T, Mitsudomi T. A resected case of large-cell neuroendocrine carcinoma of the thymus. Nihon Kokyūki Geka Gakkai Zasshi (J Jpn Assoc Chest Surg) **29**: 62-66, 2015 (in Japanese, Abstract in English).
28. Kaiho T, Iida T, Toyoda T, Fujiwara T, Hiroshima K, Shiba M. A case of neuroendocrine carcinoma of the middle mediastinum differentially diagnosed from a thymic neuroendocrine tumor. Haigan (JPN Lung Cancer) **55**: 1086-1091, 2015 (in Japanese, Abstract in English).
29. Kuroda K, Sugaya M, Shimokawa H, Matsushita A, Matsuio M, Tanaka F. A resected case of large cell neuroendocrine carcinoma in the thymus. Nihon Kokyuki Gakkaishi (Ann Jpn Respir Soc) **5**: 75-79, 2016 (in Japanese, Abstract in English).
30. Boubacar E, Atsame-Ebang G, Rabiou S, et al. Thymic large cell neuroendocrine carcinoma-a rare and aggressive tumor: a case report. J Med Case Rep **11**: 155, 2017.
31. Oda N, Miyahara N, Tabata M, et al. Pneumocystis pneumonia concomitant with ectopic ACTH syndrome caused by a large cell neuroendocrine carcinoma of the thymus. Intern Med **56**: 551-555, 2017.
32. Fabbri A, Cossa M, Sonzogni A, et al. Thymus neuroendocrine tumors with CTNNB1 gene mutations, disarrayed ß-catenin expression, and dual intra-tumor Ki-67 labeling index compartmentalization challenge the concept of secondary high-grade neuroendocrine tumor: a paradigm shift. Virchows Arch **471**: 31-47, 2017.
33. Ose N, Maeda H, Inoue M, et al. Results of treatment for thymic neuroendocrine tumours: multicentre clinicopathological study. Interact Cardiovasc Thorac Surg **26**: 18-24, 2018.
34. Ströbel P, Zettl A, Shilo K, et al. Tumor genetics and survival of thymic neuroendocrine neoplasms: a multi-institutional clinicopathologic study. Genes Chromosomes Cancer **53**: 738-749, 2014.
35. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg **251**: 1117-1121, 2010.
36. Niho S, Kenmotsu H, Sekine I, et al. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol **8**: 980-984, 2013.
37. Le Treut J, Sault MC, Lena H, et al. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large- cell neuroendocrine lung carcinoma: the GFPC 0302 study. Ann Oncol **24**: 1548-1552, 2013.