Resected thymic large cell neuroendocrine carcinoma: A case report and review of the literature

Shogo Ogata\textsuperscript{a,}, Ryo Maeda\textsuperscript{a,}, Masaki Tomita\textsuperscript{a,}\textsuperscript{*}, Yuichiro Sato\textsuperscript{b}, Takanori Ayabe\textsuperscript{a}, Kunihide Nakamura\textsuperscript{c}

\textsuperscript{a} Department of Thoracic and Breast Surgery, University of Miyazaki, Miyazaki, Japan
\textsuperscript{b} Department of Pathology, University of Miyazaki, Miyazaki, Japan
\textsuperscript{c} Department of Cardiovascular Surgery, University of Miyazaki, Miyazaki, Japan

1. Introduction

The following case report has been reported from Our University Hospital which is an internationally recognized teaching hospital and a tertiary care centre, in accordance with the SCARE guidelines for case reports \cite{1}. Large cell neuroendocrine carcinoma (LCNEC) of the thymus is a high-grade thymic tumor composed of large cells with neuroendocrine morphology and either neurosecretory granules on electron microscopy or positive neuroendocrine immunohistochemical markers \cite{2–4}. Furthermore, thymic LCNEC is an extremely rare neoplasm and has a poor prognosis \cite{2}. Because of its rarity, the detailed clinical features of thymic LCNEC remain unknown and no standard treatment has been established. In this report, we describe a surgical case of thymic LCNEC and review the cases of resection reported in the English language literature. Furthermore, we discuss the optimal therapy for this rare tumor of the thymus.

2. Presentation of case

An asymptomatic 55-year-old woman underwent a chest roentgenogram during a routine checkup; it showed an abnormal shadow in the mediastinal left upper lung field (Fig. 1). Chest computed tomography images showed a well-defined anterior mediastinal mass measuring $4.8 \times 4.0$ cm (Fig. 2). Tumor markers including carcinoembryonic antigen, cytokeratin fragment 21, progastrin-releasing peptide, $\alpha$-fetoprotein, and human chorionic gonadotropin were found to be within the normal range. Chest magnetic resonance imaging showed an iso-intensity mass on T1-weighted images and high-intensity mass on T2-weighted images, with suspected invasion to the upper lobe of the left lung (Fig. 3). Positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose (FDG) showed high FDG accumulation at the lesion [maximum standardized uptake value (SUV\textsubscript{max}) of 12.75] (Fig. 4). To avoid the incidence of tumor cell implantation and pleural recurrence after needle biopsy, we did not perform preoperative percutaneous needle biopsy. Because a malignant tumor was suspected and complete resection of the tumor was considered possible, surgical removal of the tumor through median sternotomy was performed to obtain a definitive diagnosis and achieve complete resection. Because of tumor invasion, partial resection of the left upper lobe was per-
formed. The tumor involved the left phrenic nerve; thus, the nerve was also resected.

Histopathological examination of the tumor specimen revealed tumor cells with hyperchromatic nuclei proliferating in a layered nest pattern with peripheral palisading and necrosis (Fig. 5A). Tumor emboli (Fig. 5B) or venous permeation (Fig. 5C) were frequently seen. Immunohistochemically, the tumor cells were positive for synaptophysin (Fig. 5D) and chromogranin A, but negative for cytokeratin 5/6. The postoperative histopathological diagnosis was thymic LCNEC; it was classified as a Masaoka stage III tumor due to the invasion of tumor cells into the left upper lobe. Postoperatively, the patient received adjuvant chemotherapy (4 courses of cisplatin + etoposide). She survived without any signs of recurrence for 30 months after surgery.

3. Discussion

The thymus is one of the rarest sites for occurrence of neuroendocrine tumors (NETs) (first described by Rosai and Higa in 1972 [3]), with NETs of the thymus accounting for only 2%–5% of all thymic neoplasms [4]. The latest World Health Organization thymic epithelial tumor criteria3 have classified NECs as a subtype
Fig. 3. Magnetic resonance imaging of the chest shows high intensity on T2-weighted images with suspected invasion to the upper lobe of the left lung.

Fig. 4. Positron emission tomography with 18F-fluorodeoxyglucose shows high 18F-fluorodeoxyglucose accumulation at the lesion.

Fig. 5. (A) The tumor cells with hyperchromatic nuclei proliferate in a layered nest pattern with peripheral palisading and necrosis. Tumor embolism of the left innominate vein (B) or venous permeation in the tumor (C) are found. (D) Tumor cells are immunohistochemically positive for synaptophysin.

of thymic carcinoma. Furthermore, NETs have been classified as low grade for typical carcinoids, intermediate grade for atypical carcinoids, and high-grade for LCNEC and small cell carcinomas [3]. The majority of thymic NETs are carcinoid tumors, with LCNECs account for only 14%–26% of all thymic NETs [4].

Moran et al. [5] have reported that 5-year survival rates of patients with thymic NETs were 50%, 20%, and 0% for low-grade, intermediate-grade, and high-grade tumors, respectively. In the present case, FDG-PET showed a high $SUV_{max}$. Considering the high $SUV_{max}$ and poor prognosis for high-grade NETs, thymic LCNECs were thought to have high malignant potential, likely representing thymic carcinoma. However, thymic LCNECs are extremely rare, as described above; thus, their detailed clinical features remain unknown.

To date, 19 cases of resection for thymic LCNEC have been reported in the English language literature [6–15]. The author sum-
marized a total of 20 patients, including the present case, with ages between 42 and 90 (mean age, 57) years (Table 1). Of the 20 patients, 12 (60%) were male, and the tumor size ranged from 31 to 170 mm. The tumors were classified as Masaoka stage I in 1, stage II in 1, stage III in 11, stage IVa in 3, and with stage IVb in 4 patients. Of the 20 patients, 18 (90%) had advanced-stage tumors with stage III or higher.

Of the 20 patients, 11 (55%) developed recurrence. Distant metastases were found in 9 of 11 patients. In the present case, venous permeation or tumor emboli were frequently seen in the resected specimen. In patients with lung cancer, intra-tumoral vascular invasion indicates postoperative distant metastases [16]. Because complete resection reportedly contributes to good prognosis in patients with thymic cancer [17], surgery should be recommended in patients with thymic LCNEC as well; however, surgery alone may be insufficient in such cases because of the high frequency of postoperative distant metastases.

Several studies on LCNEC of the lung have recommended postoperative administration of adjuvant chemotherapy with platinum-based combination regimens, which are used for small cell lung carcinoma that exhibits clinicopathological and biological features similar to LCNEC [18,19]. Likewise, we believe that surgery and adjuvant chemotherapy are needed to treat thymic LCNEC, even in the cases of complete resection. Although there is no evidence to support adjuvant therapy for thymic LCNEC, a regimen comprising cisplatin/carboplatin/etoposide (as for small cell lung carcinoma) seems the most common choice at present for thymic LCNEC. Therefore, adjuvant chemotherapy (4 courses of cisplatin/carboplatin/etoposide) was administered to our patient, and she survived without any signs of recurrence for 30 months after surgery. An effective therapeutic modality, combined with surgery, should be evaluated, and further studies are needed to elucidate the optimal therapy for this rare and virulent tumor of the thymus.

4. Conclusion

We reported a case of resection for thymic LCNEC. Thymic LCNEC is a highly virulent tumor of the thymus. Further accumulation of knowledge and experience is needed to elucidate the optimal therapy for this rare tumor of the thymus.

Conflict of interest

There is no conflict of interest for any of the authors.

Sources of funding

The authors state that the case report was produced in the absence of economic funding sources.

Ethical approval

Ethical approval was not required from my Institution for this case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by Editor-in-Chief of this journal on request.
Author’s contribution

Shogo Ogata and Ryo Maeda conceptualised the study, performed a literature review and drafted the manuscript.

Ryo Maeda, Masaki Tomita, Takanori Ayabe and Kunihide Nakamura performed a literature review and drafted the manuscript.

Yuichiro Sato performed a literature review and collected pathological data.

Shogo Ogata, Ryo Maeda and Masaki Tomita performed a literature review and collected data.

Shogo Ogata, Ryo Maeda and Masaki Tomita critically revised the article.

All authors approved submission of the final article.

Registration of research studies

Not applicable.

Guarantor

Masaki Tomita.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshiy, A. Fowler, D.P. Orgill, For the SCARE Group, The SCARE 2018 statement: updating consensus surgical Care EPORT (SCARE) guidelines, Int. J. Surg. 60 (2018) 132–136.

[2] T. Shoji, H. Fushimi, S. Takeda, Y. Tani, Thymic large-cell neuroendocrine carcinoma: a disease neglected in the ESMO guideline?, Ann. Oncol. 22 (11) (2011) 2535.

[3] J. Rosai, E. Higa, Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases, Cancer 29 (4) (1972) 1061–1074.

[4] W.D. Travis, E, Brambilla, A.P. Burke, A. Marx, A.G. Nicholson, WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, International Agency for Research on Cancer, Lyon, 2015.

[5] C.A. Moran, Primary neuroendocrine carcinomas of the mediastinum: review of current criteria for histopathologic diagnosis and classification, Semin. Diagn. Pathol. 22 (3) (2005) 223–229.

[6] O. Tiffet, A.C. Nicholson, G. Ladis, M.N. Sheppard, P. Goldstraw, A clinicopathologic study of 12 neuroendocrine tumors arising in the thymus, Chest 124 (1) (2003) 141–146.

[7] Y. Nagata, K. Ohno, T. Utsumi, Y. Sasaki, Y. Suzuki, Large cell neuroendocrine thymic carcinoma coexisting within large WHO type AB thymoma, Jpn. J. Thorac. Cardiovasc. Surg. 54 (6) (2006) 256–259.

[8] S. Mega, M. Oguri, R. Kawasaki, K. Hazama, K. Iwai, S. Kondo, Large-cell neuroendocrine carcinoma in the thymus, Gen. Thorac. Cardiovasc. Surg. 56 (11) (2008) 566–569.

[9] R. Dutta, A. Kumar, T. Jindal, S.R. Mathur, Neuroendocrine carcinoma of the thymus gland with sternal invasion, Interact. Cardiovasc. Thorac. Surg. 8 (6) (2009) 694–696.

[10] C. Cardillo, F. Rea, M. Lucchi, M.A. Pauli, S. Margaritorea, F. Carleo, G. Marulli, A. Musi, P. Granone, P. Graziano, Primary neuroendocrine tumors of the thymus: a multicenter experience of 35 patients, Ann. Thorac. Surg. 94 (1) (2012) 241–245.

[11] S. Aih, J.J. Lee, S.Y. Ha, C.O. Sung, J. Kim, J. Han, Clinicopathological analysis of 21 thymic neuroendocrine tumors, Korean J. Pathol. 46 (3) (2012) 221–225.

[12] Y.H. Yoon, J.H. Kim, K.H. Kim, W.K. Baek, H.K. Lee, M.H. Lee, K.H. Lee, L. Kim, Large cell neuroendocrine carcinoma of the thymus: a two-case report, Korean J. Thorac. Cardiovasc. Surg. 45 (1) (2012) 60–64.

[13] S. Igawa, N. Yanagisawa, H. Niwa, M. Ishihara, Y. Hiyoshi, S. Otani, K. Katono, J. Sasaki, Y. Sato, N. Masuda, Successful chemotherapy with carboplatin and nab-paclitaxel for thymic large cell neuroendocrine carcinoma: a case report, Oncol. Lett. 10 (6) (2015) 3519–3522.

[14] H. Domen, Y. Hida, M. Sato, H. Takahashi, T. Ishikawa, Y. Shionoya, M. Hashimoto, K. Nishiyama, Y. Aoki, K. Inoko, S. Furukawa, K. Ichinokawa, H. Yamada, Resected thymic large cell neuroendocrine carcinoma: report of a case, Surg. Case Rep. 4 (2018) 133.

[15] N. Ose, H. Maeda, M. Inoue, E. Morii, Y. Shintani, H. Matsu, H. Tada, T. Tokunaga, K. Kimura, Y. Sakamaki, Y. Takeuchi, K. Fukutomi, H. Katsura, T. Iwasaki, M. Okumura, Results of treatment for thymic neuroendocrine tumours: multicentre clinicopathological study, Interact. Cardiovasc. Thorac. Surg. 26 (1) (2018) 18–24.

[16] R. Maeda, J. Yoshida, G. Ishii, T. Hishida, M. Nishimura, K. Nagai, Prognostic impact of intratumoral vascular invasion in non-small cell lung cancer patients, Thorax 65 (12) (2010) 1092–1098.

[17] C.Y. Lee, M.K. Bae, L.K. Park, D.J. Kim, J.G. Lee, K.Y. Chung, Early Masaoka stage and complete resection is important for prognosis of thymic carcinoma: a 20-year experience at a single institution, Eur. J. Cardiothorac. Surg. 36 (1) (2009) 159–162.

[18] A. Iyoda, K. Hiroshima, Y. Moriya, Y. Takiguchi, Y. Sekine, K. Shibuya, T. Izasa, H. Kimura, Y. Nakata, T. Fujisawa, Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma, Ann. Thorac. Surg. 82 (5) (2006) 1802–1807.

[19] S. Yamazaki, I. Sekine, Y. Matsu, H. Takei, N. Yamamoto, H. Kunitoh, Y. Ohe, T. Tamura, T. Kodama, H. Asamura, R. Tsuoyi, N. Sajo, Clinical responses of large cell neuroendocrine carcinoma of the lung to cisplatin-based chemotherapy, Lung Cancer 49 (2) (2005) 217–223.

Open Access
This article is published Open Access at sciencedirect.com. It is distributed under the IJSCR Supplemental terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.