

Case Report

Pathologic diagnosis of large cell neuroendocrine carcinoma of the lung in an axillary lymph node: a case report with immunohistochemical and molecular genetic studies

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Received September 23, 2012; Accepted March 27, 2013; Epub May 15, 2013; Published June 1, 2013

Abstract: The author herein reports a large cell neuroendocrine carcinoma (LCNEC) of the lung diagnosed in an axillary lymph node without clinical data, with an emphasis of *KIT* and *PDGFRA*. A 64-year-old woman presented with axillary and cervical lymph nodes swelling. An excisional biopsy of an axillary lymph node was performed under the clinical diagnosis of malignant lymphoma. The HE section showed a presence of large malignant cells arranged in a medullary pattern. The tumor cells had nucleoli. The HE diagnosis was large cell lymphoma or metastatic undifferentiated carcinoma, in particular large cell carcinoma of the lung. The tumor cells were positive for cytokeratins, p53 protein, thyroid transcriptional factor-1, neuron-specific enolase, synaptophysin, CD56, *KIT*, and *PDGFRA*. In contrast, they were negative for CD3, CD15, CD30, CD45, CD20, CD45RO, CEA, CA19-9, and chromogranin (Dako). Ki-67 labeling (Dako) was 100%. Therefore, a diagnosis of LCNEC of the lung was made. A molecular genetic analysis for *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) identified no mutations. Later, a lung tumor and pleural effusion were detected, and the cytology of the effusion and sputum revealed carcinoma cells compatible with LCNEC. The patient was diagnosed as lung LCNEC, and treated by chemotherapy (cisplatin) and radiation (45 Gray). The present report is the first one with an examination of protein expression and gene mutations of *KIT* and *PDGFRA* in a metastatic focus of LCNEC of the lung.

Keywords: LCNEC, *KIT*, *PDGFRA*, metastasis

Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the lung is high grade neuroendocrine carcinoma composed of large cells. LCNEC shows features common to small cell carcinoma, and characterized by positive reaction to *KIT* in addition to positive neuroendocrine markers. The author herein reports an LCNEC of the lung diagnosed in an axillary lymph node without clinical data.

Case report

A 64-year-old woman presented with axillary and cervical lymph nodes swelling. An excisional biopsy of an axillary lymph node was performed under the clinical diagnosis of malignant lymphoma. The HE section showed a presence of relatively large malignant cells

arranged in a medullary pattern (**Figure 1A**). The tumor cells had nucleoli, and cell adhesion was not clear. The HE diagnosis was large cell lymphoma or metastatic undifferentiated carcinoma, in particular large cell carcinoma of the lung. Therefore, an immunohistochemical study was performed by Dako's Envision method [1]. The tumor cells were positive for cytokeratins (AE1/3 and polyclonal wide, Dako Corp., Glostrup, Denmark), p53 (almost 100%) (Dako), thyroid transcriptional factor-1 (TTF-1) (Dako) (**Figure 1B**), neuron-specific enolase (Dako), synaptophysin (Dako) (**Figure 1C**), CD56 (Dako) (**Figure 1D**), *KIT* (Dako) (**Figure 1E**), and *PDGFRA* (Santa Cruz, CA, USA) (**Figure 1F**). In contrast, they were negative for CD3 (Dako), CD15 (Dako), CD30 (Dako), CD45 (Dako), CD20 (DAKO), CD45RO (Dako), CEA (Dako), CA19-9 (TFB, Yokohama Japan), and chromogranin (Dako).

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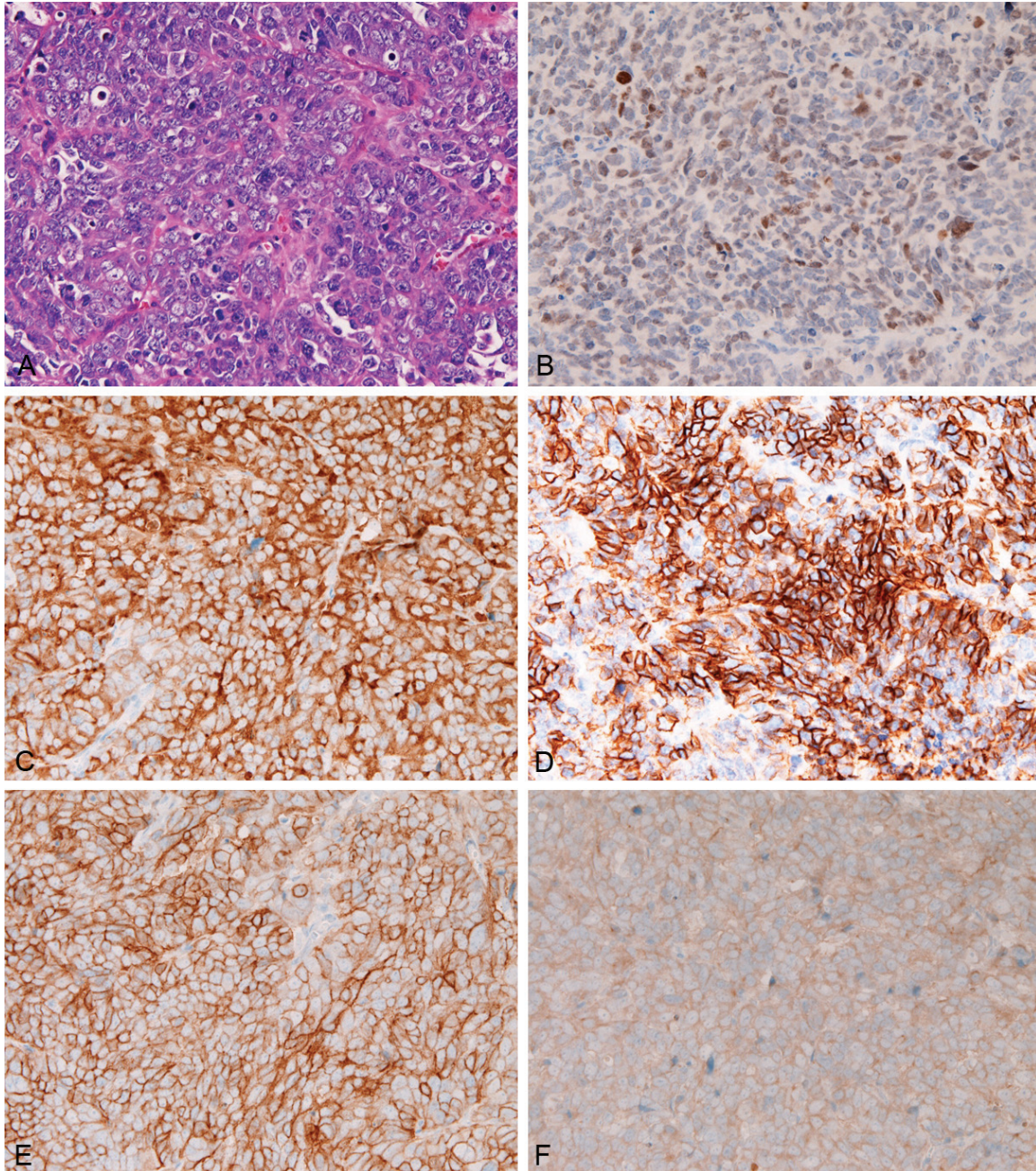


Figure 1. A: Histological findings of an axillary lymph node. The lymph node contains many areas of malignant large cells with nucleoli. Many mitotic figures are seen. Cell adhesion is not clear. HE, x200. B: TTF-1 is expressed in the nuclei. Immunostaining, x200. C: Synaptophysin is expressed in the tumor cells. Immunostaining, x200. D: CD56 is expressed in the tumor cells. Immunostaining, x200. E: KIT is expressed in the tumor cell membrane. Immunostaining, x200. F: PDGFRA is expressed in the tumor membrane. Immunostaining, x200.

Ki-67 labeling (Dako) was 100%. Therefore, a diagnosis of LCNEC of the lung was made.

A molecular genetic analysis for *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) genes was performed, in paraffin specimens, by the PCR-direct sequencing method, as previ-

ously described [2-5]. The analysis identified no mutations of the *KIT* and *PDGFRA* genes.

During the pathologic study, imaging modalities were performed and showed a right lung tumor, its metastases to mediastinal lymph nodes, and right pleural effusion. The author did not

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know these clinical findings. The cytology of the pleural effusion and sputum revealed carcinoma cells compatible with LCNEC. Lung biopsy was not performed. The patient was treated by chemotherapy (cisplatin) and radiation (45 Gray).

Discussion

LCNEC is relatively rare tumor with aggressive characters, like small cell lung carcinoma (SCLC). LCNEC and SCLC are neuroendocrine malignancies of the lungs. The differences between them are cell size and cell morphologies. The present case showed apparent neuroendocrine features, and cell morphologies were those of LCNEC. It is unique that the diagnosis of LCNEC of the lung was made by pathologic examinations of one lymph node without knowledge of clinical data in the present case.

KIT protein is frequently expressed in SCLC [6, 7] and LCNEC [8-10], as in the present case. Rossi et al. [8] reported that KIT protein was expressed in 63% of LCNEC of the lung. Sihto et al [6] reported that 30% of SCLC expressed KIT protein. *KIT* mutations are extremely rare in SCLC [6, 7]. Rossi et al [8] found no mutations in exons 9 and 11 of *KIT* gene in 83 patients with LCNEC. In the present case, *KIT* mutations in exons 9, 11, 13 and 17 were not present.

Although there have been no reports of PDGFRA protein expression in SCLC to the author's best knowledge, Sihto et al. [6] reported no *PDGFRA* mutations in 30 SCLCs. Rossi et al. [8] reported that PDGFRA expression was found in 80% of LCNEC of the lung. PDGFRA expression was seen in the present case. Sihto et al. [6] reported that no *PDGFRA* mutations were identified in 30 SCLCs. Rossi et al. [8] found no mutations in exons 12 of *PDGFRA* gene in 83 patients with LCNEC. In the present case, *PDGFRA* mutations in exons 12 and 18 were not present.

In summary, the author reported a rare case of LCNEC of the lung diagnosed in an axillary lymph node without knowledge of clinical data. The present LCNEC of the lung expressed KIT and PDGFRA proteins but were free of *KIT* and *PDGFRA* gene mutations.

Declaration

The author declares no conflict of interest.

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