Case Report

Progressive neuroendocrine tumor of lung with combined categories in metastatic site: a case report

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Background: Both large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC) are high-grade neuroendocrine tumors of lung in classification. Combined LCNEC and combined SCLC may comprise up to 25% of the resected cases. However, co-existence of LCNEC and SCLC in lung accompanied with combined LCNEC in extrapulmonary metastatic sites is infrequent.

Case Description: In this paper, we report a 58-year-old male with cough, back pain and increased sputum. He was diagnosed as LCNEC and SCLC in his lung successively. His tumor gradually progressed and combined LCNEC was then diagnosed in his cervical lymph node. Regimens of chemotherapy were accordingly adjusted several times, but his lesions were not relieved and he finally died.

Conclusions: Both LCNEC and SCLC have high aggressiveness. Some patients may have limited curative effect and poor prognosis when treated with chemotherapy even in combination with immune checkpoint inhibitors. Combined LCNEC may occur in extrapulmonary sites of some patients when the tumor progresses. Timely radiological evaluations are essential to identify changes of pulmonary and extrapulmonary lesions. Histopathological results including morphological features of malignant cells and immunohistochemical features of diseased tissues are more indispensable in establishing a confident diagnosis of lung neuroendocrine tumor and judging corresponding cellular types.

Keywords: Lung neuroendocrine tumor; classification; pathology; case report

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC) are two categories of lung neuroendocrine tumors in classification. They are high-grade tumors and have tremendous aggressiveness along with poor prognosis (1). LCNEC is usually peripherally located in the lung and has lobulated lesions, while SCLC is commonly centrally located in the major airway and has bulky lesions. Their immunohistochemical features overlap but they have quite different cellular morphology (2). Morphological features of malignant cells are therefore the main evidence of differential diagnosis. Combined LCNEC is considered when it has components of SCLC, while combined SCLC is considered when it has components of LCNEC (1). The diagnosis of combined LCNEC or combined SCLC may be decided by the main cellular components. However, LCNEC of lung followed by SCLC in lung and combined LCNEC in distant metastatic site is seldom reported.

We report here a case of high-grade lung neuroendocrine tumors in a 58-year-old male. LCNEC was initially diagnosed in lung of the patient but chemotherapy failed to hinder the progression of his tumors. SCLC in his lung and combined LCNEC in his cervical lymph node were then diagnosed in succession. This case showed the aggressiveness of high-grade lung neuroendocrine tumors and the importance of pathology in confirming their cellular

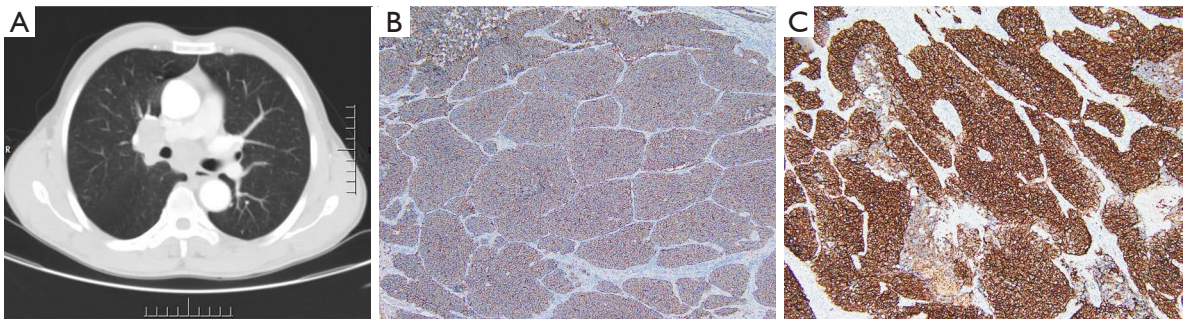

Figure 1 Radiological and histopathological images in Aug 2020. (A) A soft tissue mass of right lung was shown in chest CT scan. (B) Inferior lobe of right lung tissues were positive for Syn in immunohistochemical staining (×400). (C) Inferior lobe of right lung tissues were positive for CD56 in immunohistochemical staining (×400). CT, computed tomography; Syn, synaptophysin.

components. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2793/rc).

Case presentation

A 58-year-old male farmer admitted to our hospital in Aug 2020. He had been coughing for 40 years but was undiagnosed and untreated. On admission, the patient complained aggravated cough, back pain and increased sputum. He had a smoking history of 40 years, but denied medical histories and recent exposure to tuberculosis. Moist crackles were positive in his right lung. No abnormalities were found in remainders of the physical examination. Blood tests of our hospital showed increased carcinoembryonic antigen of higher than 200 ng/mL (normal, 0–6). Blood biochemistry, cardiac enzymes and coagulation function were nearly normal. Contrast-enhanced chest computed tomography (CT) scan showed a soft tissue mass near the hilus of right lung about 4.4 cm × 3.5 cm × 2.4 cm in size, multiple right lung nodules, enlargement of mediastinal lymph nodes, bone destruction in vertebral bodies of thoracic vertebrae (*Figure 1A*). Technetium-99m methylene diphosphonate (99mTc-MDP) bone scintigraphy showed bone destruction with increased metabolism in thoracic vertebrae, but no mass was shown in brain imaging. No bronchial stenosis was shown in fiberoptic bronchoscopy and the bronchoalveolar lavage fluid was negative for malignant cells. Resection of nodules in inferior lobe of right lung was then conducted through video-assisted thoracic surgery. These tissues were positive for malignant cells with large size in hematoxylin-eosin staining, and positive for TTF-1, synaptophysin (Syn), CD56, Ki-67 with labeling index (LI) of 90%, P53 with LI of 80% in immunohistochemical staining (*Figure 1B,1C*). The patient was therefore diagnosed as LCNEC with multiple bones and lymph nodes metastases. Antineoplastic treatments were then received by him for three cycles from Sep 2020 to Nov 2020 with intervals of approximately 3 weeks. The regimen included chemotherapy with pemetrexed/carboplatin and anti-angiogenesis therapy with bevacizumab.

In early Dec 2020, chest CT scan reevaluation revealed progression of his tumor. This was supported by enlargement of right lung soft tissue mass, involvement of more mediastinal lymph nodes and thoracic vertebrae (*Figure 2A*). Second line regimen of large cell cancer, including docetaxel and carboplatin, was used in his fourth cycle chemotherapy. Stenoses of right distal bronchi were shown in fiberoptic bronchoscopy reevaluation. Local biopsy tissues showed small cells with crush artifact in hematoxylin-eosin staining, and were positive for TTF-1, Syn, CD56, Ki-67 with LI of 100%, P53 with LI of 40% in immunohistochemical staining (*Figure 2B-2D*). This supported diagnosis of SCLC.

In late Dec 2020, chest CT scan reevaluation showed further enlargement of soft tissue mass in right lung and much more mediastinal lymph nodes involvements of the patient (*Figure 3A*). An enlarged lymph node with a diameter of 2 cm was found in his right supraclavicular fossae by palpation. This lymph node was then resected and showed malignant cells in hematoxylin-eosin staining section. These cells have mixed cellular components, including 80% large cell and 20% small cell. Immunohistochemical staining was positive for TTF-1, CgA, Syn, CD56, Ki-67 with LI of 95% and P53 with LI of 90% (*Figure 3B,3C*). These results

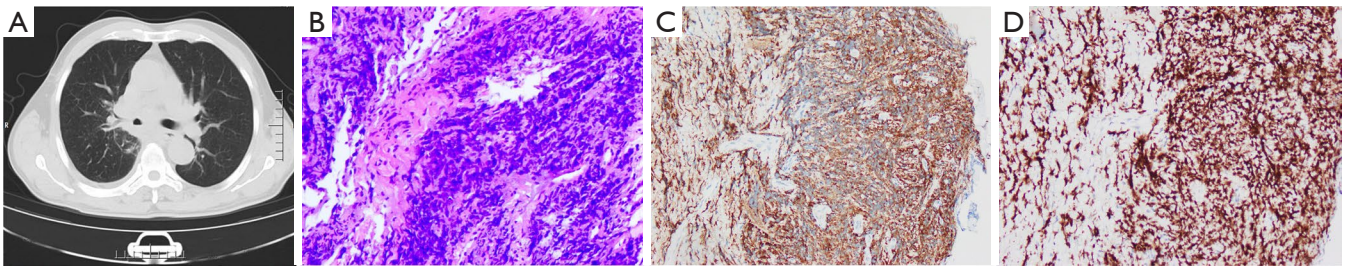

Figure 2 Radiological and histopathological images in early Dec 2020. (A) Mass enlargement was shown in chest CT scan reevaluation. (B) Right distal bronchi tissues were positive for malignant cells with small size in hematoxylin-eosin staining (×100). (C) Right distal bronchi tissues were positive for Syn in immunohistochemical staining (×100). (D) Right distal bronchi tissues were positive for Ki-67 in immunohistochemical staining (×100). CT, computed tomography; Syn, synaptophysin.

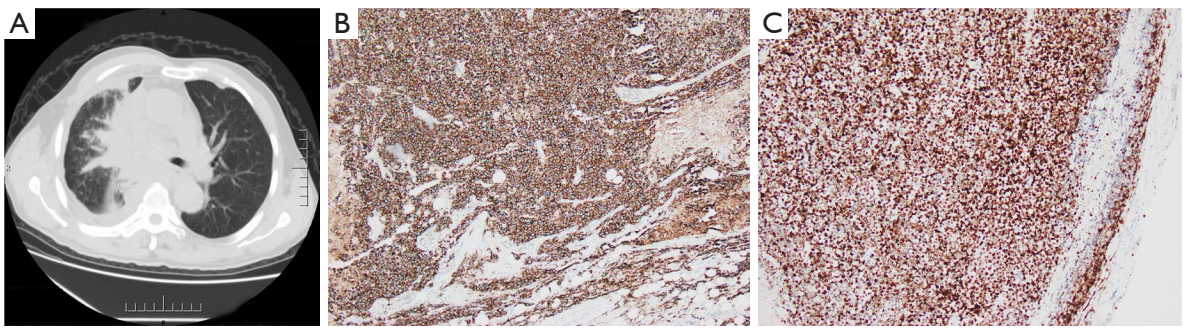

Figure 3 Radiological and histopathological images in late Dec 2020. (A) Further enlargement of mass and worse lung lesions were shown in chest CT scan reevaluation. (B) Right cervical lymph node was positive for Syn in immunohistochemical staining (×200). (C) Right cervical lymph node was positive for Ki-67 in immunohistochemical staining (×200). CT, computed tomography; Syn, synaptophysin.

supported combined LCNEC in his cervical lymph node. The patient received the fifth cycle chemotherapy with the first line regimen of small cell cancer consisting etoposide and carboplatin.

In late Jan 2021, chest CT scan reevaluation showed more serious inflammatory lesions of right lung and further enlargement of mediastinal lymph nodes. The patient then received the sixth cycle chemotherapy with another regimen of irinotecan/carboplatin. His general condition was not improved but gradually worsened. Finally, the patient refused further chemotherapy and died 2 months later.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 the editorial office of this journal.

Discussion

Lung neuroendocrine tumors are relatively rare (3). Typical carcinoid, atypical carcinoid, LCNEC and SCLC are four categories of lung neuroendocrine tumors in classification (1). Based on necrosis and mitotic rate of tumors, typical carcinoid and atypical carcinoid are respectively classified as low-grade and intermediate-grade, while LCNEC and SCLC are classified as high-grade (1). Their treatment strategies vary with categories. For example, chemotherapy is the main option for SCLC and addition of immunotherapy-based regimens may improve the prognosis (4). But the systemic treatment strategy of LCNEC has not been clearly established. Surgical resection is often the first choice in tolerant and resectable patients, while small or non-small cell lung cancer regimens are optional strategies of adjuvant chemotherapy (5). Next-generation sequencing (NGS) can determine the genomic profile of LCNEC and sub-classify

it as SCLC-like or NSCLC-like. Treatment based on this sub-classification may improve outcomes by using SCLC and NSCLC regimens based on their genomic profile (6). Other factors such as quality of care may also impact the treatment response. However, prognosis of high-grade lung neuroendocrine tumors is generally poor (7). Despite timely adjustments of treatment regimens, our reported patient still had a short overall survival. This further underlined the poor prognosis. Accurate diagnosis and classification are therefore of great importance for further management.

Both LCNEC and SCLC are highly aggressive and predominantly occur in male smokers at advanced ages (8). They often extensively present necrosis, have high mitotic rate and Ki67 proliferation index (1). But they are different in some aspects such as incidence rate, symptoms, imaging features. Compared with LCNEC, SCLC constitutes higher proportion of all lung cancers, has higher risk of paraneoplastic syndromes, more frequently occurs lymph node metastases and tumor progression when diagnosis (9-11). In radiological evaluation, LCNEC is typically peripheral lung lesions which may present lung nodules, whereas SCLC often presents central type of lung mass (12,13). But these differences are insufficient in making a definite diagnosis. Their distinction is still challenging.

In pathology, LCNEC and SCLC have overlaps in immunohistochemical staining. Both of them are positive for Syn, chromogranin, CD56, TTF-1, Ki-67. These features have therefore limited value in distinguishing SCLC from LCNEC (2,14). Their differential diagnosis remains largely morphologic dependent. SCLC is characterized by small cell size, finely granular chromatin, inconspicuous nucleoli and scanty cytoplasm (2). But LCNEC has large cell size, frequent presence of nucleoli and abundant cytoplasm (8,14).

In conclusion, both LCNEC and SCLC are high-grade lung neuroendocrine tumors. They have high aggressiveness and poor prognosis, but they generally occur in different sites of lung. In this paper, we report a rare case of high-grade lung neuroendocrine tumors. The patient was initially diagnosed as LCNEC with multiple bones and lymph nodes metastases. His tumors progressed despite three cycles chemotherapy with pemetrexed/carboplatin. SCLC was diagnosed in his right distal bronchi tissues after the fourth cycle chemotherapy with docetaxel/carboplatin. But his tumors further progressed and combined LCNEC was diagnosed in his cervical lymph node. Chemotherapy regimens accordingly adjusted but failed to hinder the progression of his tumors. This case showed the aggressiveness of high-grade lung neuroendocrine tumors. It supported timely histopathological examination to diagnose the progression and cytological types of tumors.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2793/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2793/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 the editorial office of this journal.

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