Large-cell Neuroendocrine Carcinoma of the Lung with Carcinoid Syndrome: A Case Report

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Abstract:
A 76-year-old woman was admitted to our hospital for refractory diarrhea with a poor antidiarrheal effect. Chest and abdominal computed tomography revealed a 24×22-mm mass in the left upper lobe of lung and multiple masses in the liver. Urine 5-Hydroxy indol acetic acid was markedly elevated. A liver biopsy revealed large-cell neuroendocrine carcinoma with serotonin production, suggestive of a lung origin, and a lung biopsy revealed combined large-cell neuroendocrine carcinoma and squamous cell carcinoma. Therefore, we made a definitive diagnosis of carcinoid syndrome caused by large-cell neuroendocrine carcinoma of the lung. Although chemotherapy was performed after diagnosis, the patient died 50 days postadmission.

Key words: carcinoid syndrome, large cell neuroendocrine carcinoma of the lung, refractory diarrhea

Introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung was first categorized as a high-grade neuroendocrine cell carcinoma by Travis et al. in 1991 (1). It accounts for 3% of all lung cancers, with a total age-adjusted incidence rate of 0.3/100,000 (2, 3).

Carcinoid syndrome is the most common functional syndrome, causing facial flushing, diarrhea, hypotension, and tachycardia (caused by vasoactive hormones centered on serotonin secreted by neuroendocrine tumors of the lung or digestive organs) (4). The incidence of carcinoid syndrome depends on the primary site, with carcinoid syndrome being responsible for >30% of small intestine or cecum tumors but only about 7.6% of lung tumors (5). In addition, the incidence of carcinoid syndrome in low- and intermediate-grade neuroendocrine tumors is 17.5%-22.6%, with its incidence rare in high-grade neuroendocrine tumors. Although some reports on low-grade lung neuroendocrine tumors with carcinoid syndrome are available (6), there have been no reports on LCNEC of the lung with carcinoid syndrome, except for cases of other paraneoplastic syndromes (7).

We herein report a case LCNEC of the lung with carcinoid syndrome.

Case Report

A 76-year-old woman was admitted to our hospital for refractory diarrhea with a poor antidiarrheal effect that had developed 19 days prior to presentation. She was a never-smoker and had no history of dust exposure, but her husband had smoked until 30 years ago. She was being treated for hyperthyroidism, dyslipidemia, and glaucoma. She was 153 cm tall and weighed 53 kg, and her body mass index (BMI) was 22 kg/m².

A physical examination revealed no abnormalities other than a slight fever (37.1°C) and tachycardia (107 beats/min). Chest radiography revealed an abnormal shadow in the left lung. Chest and abdominal computed tomography (CT) revealed a 24×22-mm mass in the left upper lung lobe, multiple small nodules in both lungs, some low-density areas in the liver, and mild wall thickening of the sigmoid colon (Fig. 1). Laboratory findings on admission are shown in Table 1. Levels of hepatobiliary enzymes and C-reactive protein, and fibrinolysis were increased. Although free thyroxine 4 was mildly elevated, hyperthyroidism was ruled out because thyroid-stimulating hormone levels were normal. In
addition, *Clostridium difficile* toxins were negative, and stool culture yielded normal flora.

Although her management included fasting, infusion solutions, and the discontinuation of drugs other than those for hyperthyroidism, the refractory diarrhea did not improve (with more than 20 episodes per day). Total colonoscopy showed no obvious abnormalities. We noticed temporary facial flushing one day after admission; thus, we considered carcinoid syndrome as the probable cause of the refractory diarrhea. Contrast-enhanced CT of the abdomen indicated that poorly contrasted areas occupied most of the liver, gastric pylorus, and duodenal bulb with an enhancement effect in the early contrast phase, and there were no obvious lesions in the pancreas or duodenum (Fig. 2). Upper gastrointestinal endoscopy showed that although there were no obvious abnormalities in the gastric pylorus or duodenum bulb, multiple ulcers were present in the body of the stomach; the pathological diagnosis was gastric mucosa with inflammation (Fig. 3).

Additional laboratory findings after admission are presented (Table 2). The serotonin metabolite urine 5-HIAA (5-hydroxy indole acetic acid) was markedly elevated after at
least three days of fasting and not taking any drugs that influence it; therefore, we made a definitive diagnosis of carcinoid syndrome. The elevated levels of calcitonin and serotonin were considered consistent with carcinoid syndrome symptoms. Furthermore, the decreased level of albumin in the laboratory findings on admission was considered consistent with malnutrition induced by carcinoid syndrome. Tumor markers [CEA (Carcinoembryonic antigen), CYFRA (Cytokeratin 19 fragment), NSE (Neuron specific enolase), and Pro-GRP (Pro gastrin releasing peptide)] were also markedly elevated. Thus, carcinoid syndrome was considered to have been caused by carcinoma. After subcutaneous injection of octreotide acetate, the refractory diarrhea markedly improved, reducing the frequency to less than 10 times per day.

We performed a percutaneous liver tumor biopsy and transbronchial lung tumor biopsy using ultrasound in the liver and the left upper lung lobe to diagnose the cause of the carcinoid syndrome. The pathology of the liver tumor is shown in Fig. 4. Histologically, the liver tumor infiltrated and proliferated in a palisading and nest pattern. Each tumor cell was medium to large in size and had abundant eosinophilic cytoplasm and prominent nucleoli. They also had a necrotic layer in part and showed high mitotic activity [≥11/10 high-power fields (HPFs)] and Ki-67 rate (60%). They were positive for TTF-1 (Thyroid transcription factor-1) and neuroendocrine markers, such as CD56 (Cluster of differentiation 56), synaptophysin, and chromogranin A. Therefore, we suspected primary LCNEC of the lung. They were also positive on serotonin staining.

The pathology of the lung tumor is shown in Fig. 5. Part of the lung tumor was keratinized with atypical cells suspected to be squamous cell carcinoma (SCC). This area was negative for TTF-1 and positive for CK14 (Cytokeratin14) and p40. In most of the lung tumor cells, the histological findings were similar to those of the liver. The PD-L1 (Programmed cell Death 1- Ligand 1) Tumor Proportion Score was 60%-70%; however, an EGFR (Epidermal growth factor receptor) mutation, ALK (Anaplastic lymphoma kinase) rearrangement, and ROS-1 (ROS proto-oncogene 1, receptor tyrosine kinase) rearrangement were not detected. The LCNEC area was positive on serotonin staining, but the SCC area was negative. We made a definitive diagnosis of combined LCNEC of the lung and SCC with liver metastases (cT1cN2M1c, stage IVB: Union for International Cancer Control 8th).

Bone scintigraphy and MRI (Magnetic Resonance Imaging) brain scans showed the possibility of diffuse metastases in the bone and brain. We attempted to commence chemotherapy for LCNEC of the lung, but the patient had jaundice and pedal edema because of hepatic failure, and her Eastern Cooperative Oncology Group Performance Status of 2 was worse than the value 0 at admission. We explained her medical condition and discussed potential medical treatment.
Figure 3. Upper gastrointestinal endoscopy. (a, b) No abnormality was found in the gastric pylorus or duodenal bulb. (c) Multiple gastric ulcers in the gastric body. (d) An endoscopic biopsy showed inflammatory changes (10× objective lens).

Table 2. Additional Laboratory Findings after Admission.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine 5-HIAA</td>
<td>107.6</td>
<td>0.5-5.0 mg/day</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>754.3</td>
<td>81.0-262.0 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Gastrin</td>
<td>222</td>
<td>42-200 pg/mL</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.1</td>
<td>≤0.6 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>11,003</td>
<td>≤3.91 pg/mL</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>0.43</td>
<td>0.15-1.23 ng/mL</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>3016.0</td>
<td>0.6-6.0 ng/mL</td>
<td></td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.5</td>
<td>0-37.0 U/mL</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>2.6</td>
<td>&lt;2.0 ng/mL</td>
<td></td>
</tr>
<tr>
<td>CYFRA</td>
<td>472.4</td>
<td>≤3.5 ng/mL</td>
<td></td>
</tr>
<tr>
<td>NSE</td>
<td>634.0</td>
<td>≤16.3 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Pro-GRP</td>
<td>30,998.9</td>
<td>&lt;81.0 pg/mL</td>
<td></td>
</tr>
</tbody>
</table>


with her and her family. Finally, we decided to commence chemotherapy for LCNEC of the lung with their consent, stating the possibility of her condition worsening because of chemotherapy.

Before the start of chemotherapy, she was 153 cm tall, weighed 53 kg, and had a body surface area of 1.49 m². Chemotherapy was begun with reduced standard doses of carboplatin [AUC (Area under the concentration-time curve) = 4] and etoposide (50% dose of 100 mg/m²) for LCNEC of the lung according to the small-cell lung carcinoma regimen. After chemotherapy, she developed grade 4 neutropenia and thrombocytopenia with worsened liver failure and died 50 days after admission. As her family refused, a pathological autopsy was not performed.

Discussion

We herein report a case of LCNEC of the lung with carcinoid syndrome that caused refractory diarrhea. To our knowledge, this is the first report on LCNEC of the lung with carcinoid syndrome; we therefore believe that this report is invaluable. Unfortunately, although we tried to administer chemotherapy for LCNEC of the lung, the patient had a poor prognosis because of liver failure due to liver metastasis.
Figure 4. The pathology of the liver tumor (Hematoxylin and Eosin staining are shown in a, b, c, d and immunohistochemical staining are shown in e, f, g, h). (a) Organoid, nesting, and palisading patterns in tumor cells. (10× objective lens). (b) Tumor cells showing a large size and a rich-moderate amount of cytoplasm and rare nucleolus (60× objective lens). (c) Strong view showing mitotic activity (40× objective lens). (d) Some areas of necrosis within the tumor (20× objective lens). (e) Tumor cells were positive for TTF-1, suggesting a pulmonary origin (20× objective lens). (f, g, h) Each of the markers (CD56, synaptophysin, and chromogranin A), which are characteristic of neuroendocrine tumors, were positive (10× objective lens). (i) Serotonin staining was positive (10× objective lens).

Carcinoid syndrome is a paraneoplastic syndrome caused by vasoactive hormones, such as serotonin or histamine secreted from neuroendocrine tumors, and is triggered when these hormones reach the body circulation (4). An estimated 91% of carcinoid syndrome cases are associated with liver metastases, as the hormones that are metabolized by the portal circulation of the liver exceed its metabolic capacity due to liver metastasis and flow into the body circulation in sufficient amounts (8). The incidence of carcinoid syndrome in low- and intermediate-grade neuroendocrine tumors is 17.5%-22.6%; it is rare in high-grade neuroendocrine tumors (5). In the present case, part of the LCNEC was positive for serotonin staining, and urine 5-HIAA, a major metabolite of serotonin, was significantly elevated. The positive rates of serotonin staining for LCNEC are relatively low, but we detected secretion of serotonin in the LCNEC. Therefore, carcinoid syndrome was thought to have been triggered because serotonin secreted from the LCNEC of the lung could not be sufficiently metabolized in the portal venous circulation due to advanced liver metastasis.

Lung LCNEC is often difficult to differentiate from small-cell lung cancer (SCLC) because they have very similar features. In LCNEC of the lung, the median age of the onset is 65 years old, the man-to-woman ratio is 17:1, and 98.6% of patients are smokers (2, 9); these features are similar to those of SCLC. The main difference between lung LCNEC and SCLC is tumor localization (2). On imaging tests, LCNEC of the lung, as well as non-small-cell carcinoma, is often localized at the peripheral side of the lung, whereas SCLC is often localized at the hilar or central regions of the lung. In the present case, the tumor was localized at the peripheral side. In blood tests, Pro-GRP, which is specific for SCLC, is reported to be high, especially in non-gastrointestinal neuroendocrine carcinoma, and may also be elevated in LCNEC of the lung, as seen in this case (10). In addition, calcitonin, a hormone specific to the thyroid gland, may be elevated in lung neuroendocrine tumors, as seen in this case (11).

The definitive diagnosis of LCNEC of the lung was made in the present patient based on pathology. The 2021 World
Figure 5. The pathology of the lung tumor (Hematoxylin and Eosin staining are shown in a, b, c and immunohistochemical staining are shown in d, e, f, g, h) (a) In addition to the liver tumor pathology, organoid and palisading patterns were observed in most lung tumor cells. There were also structures of keratinization with atypical cells in some lung tumor cells (10× objective lens). (b) A strong view of the tumor shows atypical cells with keratinization and cancer pearl. The periphery of the cells was relatively large and had a large amount of cytoplasm (20× objective lens). (c) Strong view shows mitotic activity (white arrowhead) (40× objective lens). (d) Tumor cells that had organoid and palisading patterns were positive for TTF-1. Tumor cells showing keratinization and atypical cells were negative for TTF-1 (10× objective lens). (e) Tumor cells showing keratinization with atypical cells and negative TTF-1 findings were positive for CK14 and p40 (10× objective lens). (f, g) Tumor cells with organoids and palisading patterns were also positive for synaptophysin and chromogranin A (10× objective lens). (h) The positivity rate of tumor cells by PD-L1 staining was approximately 60%-70% (10× objective lens). (i) Tumor cells possessing organoids and palisading patterns were positive for serotonin. Tumor cells showing keratinized structures with atypical cells were negative for serotonin (10× objective lens).

Health Organization classification is based on structural morphology, mitotic images, tumor necrosis, cytological features, and immunostaining results (12). Although it is difficult to differentiate LCNEC of the lung from SCLC, LCNEC of the lung is said to have cytological differences, such as larger individual cells, a lower N/C ratio, and clearer nucleoli than SCLC. Although surgical specimens are needed to diagnose LCNEC of the lung, we diagnosed this case as LCNEC of the lung using biopsy specimens that were recognized as having sufficient characteristic pathology. Histologically, both lung and liver specimens in this case formed organoid and fenestrated structures with active mitoses. An extensive necrotic layer was also observed in the liver specimens. Furthermore, positive immunostaining for synaptophysin and chromogranin A in both lung and liver specimens was consistent with a high-grade neuroendocrine tumor. The primary site of cancer in this case was diagnosed as the lung because both lung and liver specimens were positive for TTF-1 immunostaining. In addition, the lung specimen showed that part of the area was composed of partially keratinized atypical cells that were negative for TTF-1 and positive for CK14 and p40. Therefore, we ultimately diagnosed this case as a combined LCNEC of the lung and SCC.

Combined LCNEC of the lung is reported to account for 10.7% of LCNEC of the lung and 5.7% of LCNEC of the lung mixed with SCC (9). Clinical studies of combined LCNEC of the lung have reported that the clinical symp-
toms and prognosis are similar to those of LCNEC of the lung (13). In most cases, treatment is conducted in accordance with treatment for LCNEC of the lung.

The limitation of this case was that the pathological diagnosis was performed using a limited number of biopsy specimens. As tumor cells characterized as LCNEC of the lung secreting serotonin were recognized in both the main lesion and the metastatic lesion, we conclude that the pathology of the biopsy specimens represents the entire cohort.

We encountered a case of LCNEC of the lung with carcinoid syndrome.

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

References


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