Ectopic ACTH Syndrome Associated with Large Cell Neuroendocrine Carcinoma of the Thymus

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Abstract

A 38-year-old man was admitted for evaluation of Cushing’s syndrome. Physical findings showed swelling of the face, and hypertension, but not Cushingoid stigmata. Laboratory data revealed serum cortisol level of 34.1 μg/dL and plasma ACTH of 140 pg/mL. Overnight administration of 1 and 8 mg dexamethasone did not suppress plasma ACTH or serum cortisol. Chest X-ray showed a mass at the upper-anterior quadrant of the mediastinum, and chest CT scan revealed a heterogeneous tumor of approximately 60 mm in diameter, which infiltrated into the superior vena cava and ascending aorta, and caused superior vena cava syndrome. The tumor was resected. Histological examination indicated large cell neuroendocrine carcinoma of the thymus and positive immunoreactivity for ACTH. Ten days after the operation, the plasma ACTH decreased as low as 13.7 pg/mL. The present study indicates that large cell neuroendocrine carcinoma of the thymus can cause superior vena cava syndrome and ectopic ACTH syndrome.

Key words: ectopic ACTH syndrome, LCNEC, Cushing’s syndrome, neuroendocrine carcinoma, superior vena cava syndrome


Introduction

Neuroendocrine carcinoma of the thymus have been recently reclassified. They comprise a wide variety of histological features ranging from well-differentiated, moderately-differentiated neuroendocrine carcinoma to large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (1-4). Neuroendocrine carcinomas occur primarily in the lung, but are rare in the thymus. Since Rosai and Higa first reported neuroendocrine carcinoma in the thymus in 1972 (5), approximately 150 cases have been reported in the literature (5-7). About 15% of them were ectopic ACTH syndrome (EAS) (8). To our knowledge, no case of EAS associated with primary thymic LCNEC has been reported after neuroendocrine carcinoma was classified.

In the present study we report a patient with LCNEC of the thymus associated with EAS, who did not have any clinicopathologic feature of EAS.

Case Report

A 38-year-old man visited his local doctor because of facial and pretibial edema and hypertension. Thereafter, he complained of swelling of the face and neck and he could not wear a tie. He was examined by endoscopy of the upper gastrointestinal tract, echogram of the cervical vertebrae and measurement of blood samples. As the physician noted “moon face” in his physical findings, serum cortisol and plasma ACTH were initially measured. Because the patient exhibited an increase in serum cortisol he was suspected to have Cushing’s syndrome, and he was referred to Jichi Medical University Saitama Medical Center for further examination. Both plasma ACTH and serum cortisol were elevated to 131 pg/mL and 31.9 μg/dL, respectively, and thus he was admitted to further elucidate the presence of Cushing’s disease. He had meningitis at age 21 years. He had smoked 5 cigarettes per day for 18 years and consumed...
be. His body weight was 58 kg at 36 years, and he had gradually gained weight over 2 years.

Physical findings at the time of hospitalization showed that his height was 167 cm; body weight, 73 kg; and body mass index, 26.0. Blood pressure was 172/111 mmHg without postural change; and pulse rate, 74/min with regular rhythm. He was obese, but this was not central. There was no indication of Cushingoid stigmata, i.e., he did not have moon face, thin and fragile skin, red striae, hirsutism or petechiae. Rather his face and neck were swollen and red colored, and he exhibited edema in the lower extremities. In addition, there was no hypertensive change of Scheie in the ocular fundi.

Laboratory data showed that the white blood cells were 7530/cm³ (neutrophils, 86.0%; eosinophils, 0%; basophils, 0%; monocytes, 4.0%; and lymphocytes, 10.0%); red blood cells, 449×10⁶/cm³; hemoglobin, 15.0 g/dL; hematocrit, 43.7% and platelets, 23.2×10⁶/cm³. Serum sodium was 143 mmol/L; potassium, 3.2 mmol/L; and chloride, 102 mmol/L. Blood urea nitrogen was 13 mg/dL; serum creatinine, 0.75 mg/dL; and uric acid, 4.7 mg/dL. Fasting plasma glucose was 104 mg/dL; hemoglobin A1c, 5.3%; total cholesterol, 15.8 μg/dL, respectively. Because the invasive tumor was not totally resected, post-operative therapies were carried out, as follows: 50 Gy of radiation and 4 courses of combination chemotherapy using ADOC. However, 7 months after the operation, tumor metastasis became evident. PET-CT revealed enlarged bilateral axillary lymph nodes, right supraclavicular lymph nodes, and accumulation in the lower lobe of the left lung. At that time plasma ACTH again increased to 65.0 pg/mL. Clinical course is shown in Fig. 2.

Clinical course

Both plasma ACTH and serum cortisol levels were markedly elevated with no circadian variation. The administration of 1 and 8 mg dexamethasone did not suppress the pituitary-adrenal axis, and ACTH release did not respond to exogenous CRH. Brain MRI showed a normal pituitary gland, and chest CT showed a large thymic tumor. Thus we suggested ectopic ACTH syndrome derived from a thymic tumor. After the patient gave informed consent, the tumor was resected and the occluded superior vena cava was replaced with an artificial vessel. Ten days after the operation, plasma ACTH and serum cortisol were both normalized to 13.7 pg/mL and 15.8 μg/dL, respectively. Because the invasive tumor was not totally resected, post-operative therapies were carried out, as follows: 50 Gy of radiation and 4 courses of combination chemo-therapy using ADOC. However, 7 months after the operation, tumor metastasis became evident. PET-CT revealed enlarged bilateral axillary lymph nodes, right supraclavicular lymph nodes, and accumulation in the lower lobe of the left lung. At that time plasma ACTH again increased to 65.0 pg/mL. Clinical course is shown in Fig. 2.

Pathological findings

Macroscopic findings: The tumor originated from the thymus and invaded into the surrounding tissues, including the ascending aorta, superior vena cava, and surrounding lymph nodes in the cervical vertebrae and paraaortic tissues. Furthermore, the tumor also infiltrated into the pleura and peri-

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**Table 1.** Endocrinological Findings during the Patient’s Hospitalization

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Basal levels of various hormones</th>
<th>[ACTH, Cortisol levels at 5 pm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>140 pg/mL</td>
<td>ACTH 143 pg/mL</td>
</tr>
<tr>
<td>Cortisol</td>
<td>34.1 μg/dL</td>
<td>Cortisol 28.6 μg/dL</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>58.5 pg/mL</td>
<td>[Dexamethasone 1mg suppression test]</td>
</tr>
<tr>
<td>Renin activity</td>
<td>0.2 ng/mL/hr</td>
<td>ACTH 120 pg/mL</td>
</tr>
<tr>
<td>U. 17-OHCS</td>
<td>33.5 mg/day</td>
<td>Cortisol 23.3 μg/dL</td>
</tr>
<tr>
<td>U. 17-KS</td>
<td>32.7 mg/day</td>
<td>[Dexamethasone 8mg suppression test]</td>
</tr>
<tr>
<td>U. cortisol</td>
<td>887 μg/day</td>
<td>ACTH 149 pg/mL</td>
</tr>
<tr>
<td>Adrenalin</td>
<td>15 pg/mL</td>
<td>Cortisol 34.6 μg/dL</td>
</tr>
<tr>
<td>Noradrenalin</td>
<td>103 pg/mL</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>&lt;5 pg/mL</td>
<td></td>
</tr>
</tbody>
</table>
Microscopic findings: The thymic tumor was composed of neuroendocrine cells. The tumor cells exhibited high mitotic activity, and the nucleus/cytoplasm ratios were moderate to high, suggesting an undifferentiated tumor (Fig. 3A). Furthermore, the necrotic cells were easily found. The histological findings indicated large cell neuroendocrine carcinoma (LCNEC) according to the classification of neuroendocrine tumor (1, 9). Immunohistochemistry was performed using 4 neuroendocrine markers, namely, immunoreactivities for synaptophysin, monoclonal chromogranin and NSE were positive, but not that of CD56/NCAM. As shown in Fig. 3B, a small percentage of tumor cells exhibited positive immunoreactivity for ACTH.

Discussion

Elevation of plasma ACTH and serum cortisol was initially found in the present patient; because the local doctor noted the impression of moon face, and blood hormone levels were first measured. As noted earlier, the edematous facial change appeared rapidly, and it was derived from superior vena cava syndrome in the patient. The findings related to Cushing’s syndrome upon admission included biochemical changes of hypokalemia, hypoalbuminemia, eosinopenia and metabolic alkalosis, but did not include the physical findings of moon face, central obesity, red striae, thinned skin or hirsutism. As for Cushing’s syndrome, there was mainly biochemical derangement without any abnormal physical finding, thus indicating the early stage of EAS. As the tumor might have grown fast, the superior vena cava syndrome would have become manifest shortly thereafter in the present patient.

Since thymic carcinoid was initially described in 1972 by Rosai and Higa (5), approximately 150 cases have been reported in the literature (5-7). Recently thymic carcinoids have been reclassified as neuroendocrine carcinoma. The carcinoids comprise a wide variety of histological features ranging from well-differentiated neuroendocrine carcinomas to small cell carcinomas (1-4). Carcinoid tumors have been newly classified according to specific criteria, including the mitotic activity and the presence of necrosis or cytologic atypia. Grade I neuroendocrine carcinoma was previously described as a carcinoid tumor/well-differentiated neuroendocrine carcinoma; grade II neuroendocrine carcinoma was previously an atypical carcinoid/moderately-differentiated neuroendocrine carcinoma; and grade III neuroendocrine carcinoma previously referred to large cell neuroendocrine and small cell carcinoma (1, 9). In the present patient three neuroendocrine markers, synaptophysin, chromogranin A and NSE were positive, and histological evaluation resulted in the diagnosis of grade III neuroendocrine carcinoma/ LCNEC. Compared with neuroendocrine tumors of the lung, progressively malignant transformation is frequently observed in thymic neuroendocrine tumors and results in a
lower degree of tumor differentiation at the time of diagnosis (2). LCNEC of the thymus is very rare, and has a poor prognosis. There are only a few case reports in the literature (10-13). Ogawa et al (10) reviewed 11 Japanese cases with LCNEC of the thymus, including cases reported in meetings. The mean age was 59.0 ± 7.9 years, ranging from 46 to 67 years. In most of the patients LCNEC was diagnosed at the advanced stage, and its tumor size was ranged from 40 to 70 mm in diameter. LCNEC of the thymus re-curred 4-7 months after the initial operation in 5 of the 11 patients, similar to the present case. The cancer is somewhat associated with endocrinopathy, and in fact, EAS was verified in the present patient. de Perrot et al (8) summarized the neuroendocrine carcinoma with Cushing’s syndrome in the thymus that had been reported in 23 cases in the literature since 1972. Therefore, the present endocrinopathy is a rare pathological state derived from the thymus.

EAS was verified by several biochemical and histological findings. Immunohistochemistry revealed that ACTH immunoreactivity was sparse in the tumor cells of LCNEC. In fact, the staining using the anti-ACTH antibody was no doubt positive in several percent of the tumor cells. Plasma ACTH levels were as high as 140 pg/mL, and plasma ACTH and serum cortisol levels did not exhibit any circadian variation. An overnight administration of 1 or 8 mg dexamethasone did not suppress plasma ACTH or serum cortisol at all. While plasma ACTH levels were extremely high, the ACTH immunoreactivity seemed to be scant in the histological study. Because the tumor mass was so great, the total number of ACTH-positive cells could be quite extensive, and thus elevation of plasma ACTH may be acceptable with such a morphological feature. After the operation, both plasma ACTH and serum cortisol levels were reduced to 13.7 pg/mL and 15.8 μg/dL, respectively. This clinical course strongly supported that ACTH per se is synthesized in the LCNEC of the thymus. Furthermore, an increase in plasma ACTH levels could implicate the recurrence of neuroendocrine tumors of the thymus. In fact, plasma ACTH was elevated in the present patient 7 months after the operation, and the tumor recurrence was overt. As the LCNEC of thymus was so advanced in this patient, the operation was urgent following the diagnosis. Unfortunately, we were not able to examine hormonal responses to somatostatin analogues and bromocriptine, and thus treatment with these drugs was not performed in the present patient.

In conclusion, we report a rare case of LCNEC of the thymus that resulted in ectopic production of ACTH. The local physician initially observed “moon face” at the outpatient clinic, and ordered the tests that indicated elevation of the plasma ACTH. Superior vena cava syndrome developed progressively, and thus the tumor and the invaded tissues surrounding the tumor were all resected. Histological study revealed grade III neuroendocrine carcinoma/LCNEC and immunoreactivity for ACTH. Plasma ACTH levels could be a marker for the recurrence of LCNEC in the present patient.

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

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