Ectopic ACTH Syndrome Due to Thymic Atypical Carcinoid Treated with Combination Chemotherapy of Cisplatin and Etoposide

Toru Takahashi, Katsuhiro Hatao*, Yoshimi Yamashita** and Yukio Tanizawa

Abstract

A 21-year-old woman with Cushing’s syndrome presented with a mediastinal tumor. Ectopic ACTH syndrome was diagnosed and the tumor was resected. The histopathological diagnosis was thymic atypical carcinoid. Despite all tumor lesions having been resected, the tumor relapsed and multiple metastatic lesions grew aggressively. Combination chemotherapy with cisplatin and etoposide (VP16) was administered to control tumor progression, and achieved marked therapeutic effects. Maintenance chemotherapy with carboplatin and VP16 achieved long-term tumor control. This case indicates that some patients with atypical carcinoid tumor are good responders to chemotherapy with platinum agents and VP16.

Key words: Cushing’s syndrome, carcinoid tumor

Introduction

Ectopic ACTH syndrome was first described by Brown in 1928 (1). Many tumors, including small-cell lung carcinoma, thymoma, carcinoid, thyroid medullary carcinoma, pancreatic Langerhans cell carcinoma, and pheochromocytoma, have been reported to produce ACTH (2, 3). Among them, small-cell lung carcinomas and bronchial carcinoids are the most common and account for 55% of ectopic ACTH producing tumors, while the others are rare (2).

Here, we report a case of ectopic ACTH syndrome caused by thymic atypical carcinoid. Although most atypical carcinoids are resistant to antineoplastic agents, this case showed a good response to combination chemotherapy with cisplatin (CDDP) and etoposide (VP16).

Case Report

A 21-year-old woman was referred to our hospital in July 1999, complaining of facial edema, acne, and an irregular menstrual period. She was obese and her face was moon-like. There was a buffalo hump in her upper back, but no other significant findings were noted on physical examination. Endocrinological examinations revealed her plasma ACTH level at rest in the morning to be 180 pg/ml, plasma cortisol 25.7 µg/dl, and urinary 17-OHCS 11.5 mg/day. Urinary 17-KS and basal levels of other pituitary hormones were normal (Table 1). Plasma cortisol was not suppressed.

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Peripheral blood</th>
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<tbody>
<tr>
<td>TP 7.7 g/dl</td>
<td>RBC 454x10^6/µl</td>
</tr>
<tr>
<td>Alb 4.4 g/dl</td>
<td>Hb 14.3 g/dl</td>
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<tr>
<td>T. Bil 0.6 mg/dl</td>
<td>Plt 18.6x10^9/µl</td>
</tr>
<tr>
<td>AST 20 IU/µl</td>
<td>WBC 12,500/µl</td>
</tr>
<tr>
<td>ALT 30 IU/µl</td>
<td>Neutro. 78%</td>
</tr>
<tr>
<td>LDH 686 IU/µl</td>
<td>Eosino. 0%</td>
</tr>
<tr>
<td>ALP 280 IU/µl</td>
<td>Baso. 0%</td>
</tr>
<tr>
<td>GTP 24 IU/µl</td>
<td>Lympho. 16%</td>
</tr>
<tr>
<td>BUN 10.3 mg/dl</td>
<td>Mono. 6%</td>
</tr>
<tr>
<td>Cr 0.7 mg/dl</td>
<td>Endocrinological examinations</td>
</tr>
<tr>
<td>CRP 0.1 mg/dl</td>
<td>ACTH 180 pg/ml</td>
</tr>
<tr>
<td>Na 139 mmol/l</td>
<td>Cortisol 25.7 µg/dl</td>
</tr>
<tr>
<td>K 3.9 mmol/l</td>
<td>Urinary 17-OHCS 11.5 mg/day</td>
</tr>
<tr>
<td>Cl 102 mmol/l</td>
<td>Urinary 17-KS 5.3 mg/day</td>
</tr>
</tbody>
</table>

Table 1. Laboratory Data on Admission

Tumor markers

| NSE 8.5 ng/ml |
| Serotonin 0.05 µg/ml |

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Peripheral blood counts and biochemical studies are summarized in Table 1. Serum lactate dehydrogenase (LDH) was elevated. There was no hypokalemia. Chest X-ray and magnetic resonance imaging showed a large mass in the anterior mediastinum (Fig. 1). There were neither pulmonary nodular lesions nor pleural effusion. Head and abdominal computed tomography (CT) scans were normal.

The diagnosis of ectopic ACTH syndrome was made and the mediastinal mass was suspected to be an ACTH-producing tumor. Since there were no apparent metastatic lesions in the imaging studies, the tumor was resected in August 1999. Intraoperatively, however, several lesions invading the pleura, epicardium, and right diaphragm were observed. All of these macroscopic invasive lesions were resected together. The histopathological examination revealed the tumor cells to have grown in a trabecular pattern with mitoses and rosette formation, showing the characteristics of a neuroendocrine tumor (Fig. 2). Since the tumor accompanied normal thymus tissue, thymic atypical carcinoid was diagnosed. Postoperatively, plasma ACTH and cortisol levels fell rapidly to within the normal range. She recovered uneventfully and was discharged two weeks later.

Two months after surgery, however, follow-up CT scan revealed small recurrent nodules in the right interlobar pleura. The nodular lesions progressed rapidly, and other disseminated nodules became apparent in the pleura and on the right diaphragm (Fig. 3A). ACTH and LDH levels increased and Cushing’s symptoms, such as facial edema, acne, and hypokalemia reappeared. Aggressive progression of the disseminated lesions caused massive pleural effusion and dyspnea (Fig. 3B). Combination chemotherapies were considered, and the patient was administered CDDP 40 mg/m²/day and VP16 100 mg/m²/day intravenously on days 1 to 5 every 4 weeks. After three courses of this therapy, the pleural effusion disappeared completely, the tumor shrank (Fig. 3C), and ACTH and LDH levels decreased. Grade 3 neutropenia (neutrophils ≥1,200/μl), thrombocytopenia (Platelets ≥38,000/μl), and grade 2 nausea were observed, but there were no other significant side effects. No renal function impairment was seen during three courses of therapy. Although the treatment was effective, one lesion in the interlobar pleura did not disappear completely (Fig. 3C). Therefore, we considered achieving complete remission with chemotherapy to be difficult. She was discharged, free of clinical symptoms, in March 2000. As maintenance therapy,
Chemotherapy for Thymic Atypical Carcinoid

Figure 3. Computed tomographic scans of the relapsed tumor. (A) In December 1999 (3 months after resection), several nodal tumors are seen on the right interlobar and parietal pleura. (B) In January 2000, rapid growth of multiple metastatic tumors and massive right pleural effusion are apparent. (C) In March 2000, the pleural effusion disappeared and the tumor shrank after 3 courses of chemotherapy.

we employed a less toxic carboplatin dose of 300 mg/m² with VP16 120 mg/m² every 2 or 3 weeks, and good tumor control was achieved for nine months.

In December 2000, the tumor again showed gradual progression with increases in ACTH and LDH levels. Mitotane (o, p'-DDD) was administered in January 2001 and radiotherapy for the main thoracic tumor to achieve palliative mass reduction, but with limited effectiveness. To control hypercortisolemia, bilateral adrenalectomy was performed in May 2001. Although adrenalectomy corrected the hypercortisolemia, the metastatic tumor became chemotherapy resistant and progressed rapidly. In February 2002, she died of systemic metastasis and multiple organ failure. The clinical course of our case is summarized in Fig. 4.

Discussion

Ectopic ACTH producing tumors are observed in about 10% of Cushing’s syndrome cases (2, 3). The acute type of ectopic ACTH syndrome is known to often be associated with small-cell lung carcinoma while the chronic type is associated with carcinoids. The type of clinical manifestation depends on the rate of tumor progression (2). The present thymic carcinoid case showed aggressive progression and hypercortisolemia symptoms developed rapidly, especially during the period of post-operative relapse.

Carcinoid tumors are considered to arise from neuroendocrine cells. The primary sites of most carcinoids are within the gastrointestinal tract, e.g. the appendix, ileum, rectum, and stomach. The incidence of bronchial carcinoids is about 10%, while that of thymic carcinoids is less than 5% (4). Histopathologically, carcinoids with more nuclear atypia, higher mitotic activity, and focal necrosis are classified as atypical carcinoids. Although most carcinoids are indolent, atypical carcinoids, as in our case, are known to be more aggressive and malignant than their typical counterparts.
It was not particularly difficult to make the clinical diagnosis of ectopic ACTH syndrome in this case, because she had an apparent mediastinal tumor, elevated ACTH, and typical symptomatic hypercortisolemia which was not suppressed by the overnight 8 mg dexamethasone test. The diagnosis was confirmed by the rapid decrease in plasma ACTH after tumor resection. The clinical course of her atypical carcinoid was very aggressive. Although disseminated lesions in the pleura and diaphragm were all resected intraoperatively, relapse was seen only 2 months after the operation. Since the disseminated lesions were diffuse and multiple, systemic chemotherapy was the only option for controlling tumor progression. In general, carcinoid tumors are indolent. For isolated tumors, surgical resection is the treatment of choice. However, with dissemination, treatment is difficult.

Several chemotherapeutic regimens including streptozocin, cyclophosphamide, fluorouracil, and/or doxorubicin have been reported for metastatic carcinoids. The response rates to those chemotherapies seldom exceeded 30%, and complete responses were uncommon (4–7). Two reported cases of thymic carcinoid with ectopic ACTH syndrome were refractory to chemotherapy (8, 9). However, for metastatic atypical carcinoids only, a high response rate (67%) has been reported with combination chemotherapy employing CDDP and VP16 (10).

We obtained informed consent from the patient and administered combination chemotherapy with CDDP and VP16. We used higher doses of the chemotherapeutic agents than in the original regimen reported by Moertel et al (10) to strengthen the dose intensity, as advocated by Trump et al (11). The intensified combination chemotherapy was safe and effective, allowing the patient to be discharged from the hospital without symptoms. Both the primary combination chemotherapy and the following maintenance therapy, administered in the outpatient setting, were tolerable. Although complete remission was not obtained, it is noteworthy that long-term tumor control was achieved with chemotherapy in this highly aggressive carcinoid.

There is no standard therapy for metastatic carcinoids. The efficacy of chemotherapy has not been well established and it is difficult to perform a large-scale randomized trial for such a rare disease. However, there are clearly cases like the present case who are good responders to antineoplastic agents, especially to regimens including platinum agents and VP16.

References

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Chemotherapy for Thymic Atypical Carcinoid


