Aggressive course of carcinoma showing thymus-like differentiation with distant metastasis and temporary activity of cisplatin and irinotecan

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Abstract

Introduction

Carcinoma showing thymus-like differentiation is a rare type of thyroid cancer arising from a remnant of thymic epithelium. Patients with carcinoma showing thymus-like differentiation have a relatively better prognosis when diagnosed in the early stage. Surgery plays a crucial role, and patients with metastatic carcinoma showing thymus-like differentiation are treated with chemotherapy; however, metastatic carcinoma showing thymus-like differentiation is reported to be refractory to chemotherapy.

Case report

A 54-year-old male patient presented with hoarseness and a left cervical tumour. The patient was histologically diagnosed with squamous cell carcinoma by a needle biopsy specimen from a left inferior thyroid tumour. Immunohistochemistry studies showed that the specimen stained positive for CD5, slightly stained positive for CD117 (cKIT), and negative for CD5, slightly stained positive for CD117 (cKIT), and negative for thyroglobulin, thyroid transcription factor 1 and calcitonin. The tumour therefore seemed to be a carcinoma arising from thymic epithelium. A computed tomography scan revealed the primary site to arise from the left inferior thyroid. The patient was diagnosed with metastatic carcinoma showing thymus-like differentiation involving the lungs, liver and brain. Four cycles of cisplatin and irinotecan combination chemotherapy were administered according to the front-line chemotherapy protocol for thymic carcinoma. The chemotherapy had a significant beneficial effect, such that the patient’s general condition improved and he returned to work. However, the patient died five months after initiating chemotherapy because of rapid tumour progression.

Introduction

Carcinoma showing thymus-like differentiation (CASTLE), sometimes called ectopic thymic carcinoma, is a rare cancer arising from an ectopic thymic remnant in the inferior thyroid because of abnormal migration during foetal development; both thymic tissue and parathyroid tissue arise from the third and fourth pharyngeal pouches. During normal foetal development, thymic epithelial tissue migrates down to the mediastinum along the thymic line. In CASTLE, however, the thymic epithelial tissue remains in the thyroid, and the thymic remnant becomes malignant. At present, thymoma in the neck is classified into four groups. Benign thymoma is classified as ectopic hamartomatous thymoma and ectopic thymoma. Thymic carcinoma is classified as spindle epithelial tumour with thymus-like differentiation and CASTLE; these latter two groups are relevant to thymic carcinoma.

Intrathyphic thymoma and intrathyphic carcinoma are apparently distinguished from one another according to the 2004 World Health Organization (WHO) classification¹. Thus, the response to chemotherapy is reported to differ between thymoma and thymic carcinoma².

Because of the rarity of CASTLE, no consensus on its clinical management has been reached, including its staging and treatment. The only published report on the treatment for CASTLE has been that of response to chemotherapy by a patient with relapsed CASTLE who was treated with cisplatin and docetaxel³.

The case of a patient with metastatic CASTLE with a remarkable response to chemotherapy but an aggressive course is reported.

Case report

A 54-year-old man was referred to the Tokyo Metropolitan Cancer and Infectious Diseases centre at Komagome Hospital (Tokyo, Japan) with complaints of hoarseness and a left cervical tumour. The patient had been smoking 1 pack of cigarettes per day for the last 40 years. On physical examination, a palpable left cervical tumour was apparent. Serum levels of thyroid-stimulating hormone and calcitonin were within normal (1.77 μU/mL and 33 pg/mL, respectively). An elevated serum cytokeratin fragment of 20 ng/mL, squamous cell carcinoma (SCC) antigen of 2.1 ng/mL and carcinoembryonic antigen (CEA) of 45.5 ng/mL were found. Contrast-enhanced
Computed tomography (CT) scanning of the neck and abdomen demonstrated a tumour that was 4.5 cm in size from the left inferior thyroid to the superior mediastinum that caused the trachea to deviate to the left side. CT and magnetic resonance imaging also demonstrated multiple pulmonary, hepatic and cerebral metastases (Figures 1A, 1B and 1C). Echocardiography suggested a malignant tumour of the thyroid (Figure 2A), and scintigraphy suggested possible thyroid metastasis from another organ (Figure 2B). The patient underwent an excisional biopsy of the enlarged thyroid tumour; histopathological examination revealed that the patient was suffering from SCC. At the same time, immunohistochemistry showed that the specimen stained positive for CD5 (Figure 3A and 3B) and slightly positive for CD117 (c-KIT). Thyroglobulin, thyroid transcription factor 1 and calcitonin were negative. These characteristics were consistent with SCC of thymic origin; thus, the most likely diagnosis was CASTLE. The patient was initially treated with cisplatin 80 mg/m² (day 1) and irinotecan 60 mg/m² (days 1, 8 and 15) every four weeks as a cycle of chemotherapy. Haematological and other toxicities were equivalent to grade 2. Chemotherapy produced a partial response (58.7% in the Response Evaluation Criteria in Solid Tumours version 1.1) for at least four months (Figure 1D, 1E and 1F) and improved the patient’s ability to perform daily activities. At the fifth month after the initiation of chemotherapy, his condition worsened, with dehydration, renal dysfunction and brain metastasis, with a performance status of 4 because of unexpected rapid progression of the cancer. The patient died of cachexia within two weeks, without proceeding to second-line chemotherapy.

**Discussion**

This patient with CASTLE was treated with the same type of chemotherapy as for thymic carcinoma. This illustrates that the chemotherapeutic regimen for thymic carcinoma is potentially useful for patients with metastatic CASTLE with regard to both efficacy and tolerability. In 1984, Rosai et al. first reported ‘ectopic hamartomatous thymoma’ to be an ectopic thymic epithelial tumour derived from the third pharyngeal pouch, occurring in the suprasternal or supraclavicular inferior neck. In 1991, Chan and Rosai classified these tumours into four subtypes of thymus-like differentiated tumour, including ectopic cervical thymoma and CASTLE. In 2004, CASTLE was definitively designated as an independent clinicopathological entity of thyroid tumour in the WHO classification. Thus, it is natural for CASTLE to share the same histological category as thymic carcinoma, which causes the diagnosis to be challenging. To diagnose thymic-derived malignant tumour, immunohistochemical staining (CD5, c-KIT) is useful because of its specificity and sensitivity. To distinguish CASTLE from other types of thyroid neoplasms, CD5, high molecular weight keratin, CEA and p63 appear...
Figure 3: Ultrasonography of the neck demonstrates a significantly enlarged inferior left lobe of the thyroid with a heterogeneous hypoechoic pattern. Much particle calcification is present in the peripheral area, and decreased blood flow is seen in the tumour. (A) Anterior neck scan using Tc-99m shows no defect. The scan with Ti-201 shows poor accumulation in the tumour, but there is accumulation in the lymph nodes (B).

Table 1. Reported patients treated with palliative-intent chemotherapy for advanced carcinoma showing thymus-like differentiation.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Age (years), Gender</th>
<th>Chemotherapy</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakudo, 1985</td>
<td>59, male</td>
<td>Doxorubicin + cyclophosphamide + ACNU</td>
<td>Minor response*</td>
</tr>
<tr>
<td>Roka, 2004</td>
<td>31, male</td>
<td>Cisplatin 60 mg/m² + docetaxel 75 mg/m²</td>
<td>CR*</td>
</tr>
<tr>
<td></td>
<td>48, female</td>
<td>¹Cisplatin 30 mg/m² + epirubicin 75 mg/m²</td>
<td>PD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>²Liposomal doxorubicin 60 mg/m²</td>
<td>PD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>³Irinotecan 80 mg/m²</td>
<td>PD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>⁴Docetaxel 75 mg/m²</td>
<td>PD*</td>
</tr>
<tr>
<td>Kusada, 2005</td>
<td>68, male</td>
<td>Paclitaxel</td>
<td>PD*</td>
</tr>
<tr>
<td>Cappelli, 2007</td>
<td>73, male</td>
<td>Cisplatin 50 mg/m² + doxorubicin 45 mg/m² + cyclophosphamide 600 mg/m²</td>
<td>None (toxic death)</td>
</tr>
<tr>
<td>Steger, 2009</td>
<td>62, male</td>
<td>¹Doxorubicin + cisplatin + cyclophosphamide</td>
<td>SD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>²Doxorubicin + cisplatin + cyclophosphamide</td>
<td>PD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>³Imatinib</td>
<td>PD*</td>
</tr>
<tr>
<td>Present patient</td>
<td>54, male</td>
<td>Cisplatin 80 mg/m² and irinotecan 60 mg/m²</td>
<td>PR</td>
</tr>
</tbody>
</table>

*All reported cases, excluding the present patient, were not always evaluated by RECIST criteria version 1.1.

ACNU, nimustine; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

The superscripted numbers imply the lines of chemotherapy.

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to be useful. In the present patient, CASTLE was diagnosed because of the extensive nature of the mass. The diagnosis was easily determined with immunohistochemical staining. The optimal staging or treatment for this disease is not known because of its rarity. However, since CASTLE originates from thymic tissues, staging or treatment could be based on the Masaoka-Koga staging system, which was developed for thymic epithelial tumours. Furthermore, as with CASTLE, the optimal treatment for thymic carcinoma has not been determined because of its rarity. To date, less than 30 cases of CASTLE have been documented, including only four metastatic cases (with distant metastasis). Optimal chemotherapy has also not been determined. Among patients reported to receive anthracycline-based chemotherapy, such as doxorubicin/cyclophosphamide/nimustine (ACNU) or doxorubicin/cisplatin/cyclophosphamide (PAC), no case with clinical response has been reported. However, Roka et al. reported the only patient who had clinical response, in whom cisplatin 60 mg/m² and docetaxel 75 mg/m² produced a complete response. The present patient received cisplatin and irinotecan combination chemotherapy according to the treatment approach for intrathymic thymic carcinoma. The tolerability and efficacy of this chemotherapy regimen were good. Nonetheless, it is reasonable that the chemotherapeutic strategy for thymic carcinoma is suitable for metastatic CASTLE because they share the same biological basis, as mentioned earlier. In addition, although thymic carcinoma has been placed in the same category as thymoma, recent investigations have demonstrated that thymic carcinoma and thymoma are apparently different clinical entities. Thus, cisplatin, but not necessarily anthracycline, plays a key role in treating metastatic thymic carcinoma. In the later lines of chemotherapy, a single-agent chemotherapy regimen, such as gemcitabine or S-1, has the potential to be effective, according to the chemotherapy regimen for thymic carcinoma.

The rarity of these types of cancers provides insufficient numbers of patients and, thus, limited clinical evidence to allow realistic clinical verification of different treatment strategies. It is to be hoped that longer follow-up periods might be available in the future to enable evaluation of treatments for these rare cancers.

Abbreviations list

CASTLE, carcinoma showing thymus-like differentiation; CEA, carci-noembryonic antigen; CT, computed tomography; SCC, squamous cell carcinoma; WHO, World Health Organization.

References