Small Cell Carcinoma of the Esophagus: a Case Report

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This article reports a case of primary undifferentiated small cell carcinoma of the esophagus with lymph node metastasis which invaded the stomach wall. The patient was treated with chemotherapy alone, consisting of CDDP and VP-16. The patient had a complete response to chemotherapy, with no evidence of disease for nine months, after six courses of the regimen. Small cell carcinoma of the esophagus is an aggressive tumor with an extremely poor prognosis. Because its characteristics are similar to small cell carcinoma of the lung, small cell carcinoma of the esophagus should be treated by multi-drug chemotherapy including CDDP, with or without radiation as the first line treatment. This chemotherapy regimen may achieve a long disease-free survival time.

Key words: esophagus – small cell carcinoma – chemotherapy

INTRODUCTION

The most common histological type of primary esophageal neoplasm is squamous cell carcinoma; other types are rare. Among them, small cell carcinoma (SCC) is an extremely rare tumor and fewer than 200 cases have been reported worldwide as of 1995. SCC of the esophagus has characteristics similar to SCC of the lung: early dissemination and a dismal prognosis. Although the reported cases of esophageal SCC have been treated by various means, including surgical resection, radiation, chemotherapy and combinations of therapy, the tumors were so aggressive that the prognosis and outcome were always poor.

We recently encountered a 63-year-old man with primary SCC of the esophagus with lymph node metastasis which invaded the stomach wall. He responded to chemotherapy and is now in good condition with no evidence of disease.

CASE REPORT

A 63-year-old man who had a two-month history of dysphasia and weight loss (5 kg) was referred to the National Shikoku Cancer Center Hospital in March 1995 after esophageal and gastric tumors were discovered during endoscopic investigation of the dysphasia. He had smoked one and a half packs of cigarettes per day and had drunk 500 ml of Japanese wine per day for 30 years. Physical examination revealed no abnormality. The supraclavicular lymph node was not palpable, anemia and jaundice were not observed and hypertension was controlled by a calcium blocker. A chest x-ray showed no abnormal shadow and laboratory values were within normal limits. Tumor markers were also within normal limits: CEA 3.5 ng/ml (normal value <5 ng/ml), CA 19-9 <1.8 U/ml (normal value <370 U/ml), squamous cell carcinoma antigen 0.5 ng/ml (normal value <1.5 ng/ml) and neuron-specific enolase (NSE) 6.4 ng/ml (normal value <10.0 ng/ml). Serum adrenocorticotropic hormone (ACTH) was 37 pg/ml (normal value <60 pg/ml). A barium swallow showed an elevated tumor with ulceration in the midthoracic esophagus (Fig. 1(a)) and ulceration with extraluminal compression in the gastric cardia immediately beneath the esophago-gastric junction, without any obstructive findings. Upper gastrointestinal endoscopy revealed an elevated lesion with deep excava tive ulceration on the anterior wall of the esophagus 30 cm from the incisor and an irregularly-shaped reddish flat lesion on the posterior wall of the esophagus (Fig. 2(a)). The endoscopy also revealed an ulcerative lesion with extraluminal compression on the lesser curvature of the gastric cardia.

The biopsy specimens from the esophageal elevated lesion and gastric ulcerative lesion demonstrated the following histological findings: small hyperchromatic cells with scanty cytoplasm, nuclear molding and inconspicuous nucleoli, arranged in solid sheets and also in a ribbon pattern (Fig. 3). On Grimelius staining, argiophilic cells were observed, and they were mostly positive for neuron-specific enolase (NSE), but neurosecretory granules were not demonstrated by repeated electron microscopy. Based on these findings, we diagnosed these tumors to be SCCs. Biopsy specimens from the reddish flat lesion confirmed squamous cell carcinoma. A thoracic CT scan revealed a midthoracic esophageal mass without any abnormal finding in pulmonary and mediastinal lesions. Abdominal CT scan showed a low-density mass 4 cm in size on the right side of the lesser curvature of the gastric cardia (Fig. 4(a)). Bronchoscopy showed mild compression of the left bronchus with slight redness and a biopsy specimen revealed no
Small Cell Carcinoma of the Esophagus

Figure 1. (a) Barium swallow showing elevated tumor with ulceration in the midthoracic esophagus. (b) After the third course of chemotherapy, the barium esophagogram was normal.

Figure 2. (a) Upper gastrointestinal endoscopy revealing an elevated lesion with deep excavative ulceration on the anterior wall of the esophagus 30 cm from the incisor, and an irregularly-shaped reddish Lugol unstained flat lesion on the posterior wall of the esophagus. (b) After the third course of chemotherapy, the tumor had disappeared and normal mucosa was observed.

malignancy. Bone scintigram and brain CT scan showed no metastatic lesion, nor did aspirate of bone marrow.

Under the diagnosis of advanced primary SCC of the esophagus with lymph node metastasis which invaded the gastric cardia, combination chemotherapy was begun. It consisted of cis-dichlorodiammine platinum (II) (CDDP) 80 mg/m² on day 1 and 70 mg/m² of etoposide (VP-16) on days 1–4, beginning on March 16 1995, both given intravenously. After the first course of this regimen, the patient’s dysphasia had resolved and the tumor size was reduced on gastrointestinal examination. We administered three courses of this regimen during his admission and observed marked symptomatic improvement. After the third course of chemotherapy, a repeat barium esophagogram was normal (Fig. 1 (b)) and endoscopy showed normal esophageal mucosa (Fig. 2 (b)) with only some small Lugol unstained flat lesions on the anterior wall of the esophagus and a reduction in the size of the ulcerative lesion on the gastric cardia. Biopsy specimens of the lesion showed no malignancy. On abdominal CT scan, the mass on the right side of the gastric cardia was completely healed (Fig. 4 (b)). The reservoir of a central venous catheter was implanted subcutaneously in the right chest wall for further chemotherapy, and the patient was admitted and discharged three more times to receive the treatment. A total of six courses of chemotherapy were given, ending in November 1995.

At the time of writing this report, the patient remains asymptomatic, and the results of physical examinations are
unchanged. Granulocytopenia (Grade 1) (1) appears each time but with no significant complication. Laboratory data were all normal at the time of discharge after his sixth course of treatment: WBC 5600/µl, RBC 381 × 10^6/µl, Hb 11.4 g/dl, platelets 20.8 × 10^4/µl, GOT 20 IU/l, GPT 17 IU/l, LDH 298 IU/l, ALP 216 IU/l and LAP 41 IU/l. The renal function remained within normal limits (creatinine clearance 84 ml/min, serum creatinine 1.1 mg/dl). The patient is in good condition with no evidence of the disease nine months after the start of chemotherapy.

REVIEW OF THE LITERATURE

It is clear from previous reports of SCC of the esophagus that the prognosis for this carcinoma is extremely poor, and a standard treatment method has not been established. We reviewed previous treatment methods for esophageal SCC and their results to determine the best way to treat this SCC. We reviewed 60 reports, from 1952 to 1995, which included 145 cases of SCC of the esophagus, and we investigated the 89 cases which described the treatment and prognosis in detail.

The patients were 71 men and 18 women whose ages ranged from 40 to 85 years (mean 63.2 years at diagnosis). Five of the 89 cases were excluded because of perioperative death. Eighty-four cases remained for statistical evaluation and were divided into six groups according to the method of treatment. Group 1 comprised untreated cases because of poor condition with disseminated disease at first visit to hospital (n = 14, male 10, female 4). Group 2 patients received chemotherapy alone (n = 23, male 18, female 5). Group 3 received radiotherapy alone (n = 6, male 6, female 0). Group 4 received chemo- and radiotherapy (n = 11, male 8, female 3). Group 5 had operation alone (n = 10, male 8, female 2). Group 6 had operation with pre- and/or postoperative chemo- and/or radiotherapy (n = 20, male 16, female 4).

The survival curve was calculated by the Kaplan-Meier method (2), and the significance of difference in survival times was analyzed by the log rank test, with significance defined as P < 0.01. The prognostic significance was analyzed by Cox’s proportional hazard model. The parameters were age, sex and the treatment methods: operation, chemotherapy and radiotherapy.

The survival curve of the 84 cases is shown in Fig. 5. The mean 50% survival time of all cases was 6 months. The characteristics of each treatment method group of and the 50% survival times are shown in Table 1, and the survival curves are shown in Fig. 6. The prognosis was extremely poor when untreated; almost of all these patients died within a month. Significant differences were observed as follows: Group 1 vs. any other group, P ≤ 0.001; Group 2 vs. Group 6, P = 0.009; Group 3 vs. Group 6, P = 0.0035.

<table>
<thead>
<tr>
<th>Group</th>
<th>First treatment</th>
<th>No. of cases</th>
<th>50% survival (months)</th>
<th>P value (vs group 1)</th>
<th>P value (vs group 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>14</td>
<td>1</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>2</td>
<td>Chemotherapy alone</td>
<td>23</td>
<td>7</td>
<td>0.001</td>
<td>0.0035</td>
</tr>
<tr>
<td>3</td>
<td>Radiotherapy alone</td>
<td>16</td>
<td>4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>Chemoradiotherapy</td>
<td>11</td>
<td>7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>Operation alone</td>
<td>10</td>
<td>6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>Combined therapy with surgical resection</td>
<td>20</td>
<td>8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>84</td>
<td>6</td>
<td></td>
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</tbody>
</table>
The prognostic significance of operation, chemotherapy and radiotherapy as the treatment methods and additionally age and sex through multivariate analysis by Cox’s proportional hazard model are shown in Table 2. Age and sex did not affect prognosis, but all methods of treatment improved the prognosis significantly: operation, $P = 0.002$; chemotherapy, $P < 0.001$; radiotherapy, $P = 0.0036$.

**DISCUSSION**

Primary undifferentiated small cell carcinoma is a rare histological type of esophageal carcinoma. Since McKeown (3) first described two autopsy cases of esophageal SCC as oat cell carcinoma in 1952, fewer than 200 cases have been reported as of 1995, variously termed oat cell carcinoma, ACTH-producing tumor, anaplastic carcinoma, APUD (amine precursor and dehydroxylation) tumor or undifferentiated small cell carcinoma.

Primary SCC of the esophagus is clinically a very aggressive tumor, and most of the patients who present with an advanced stage have a poor prognosis. The reported cases of SCC of the esophagus have been treated with various forms of treatment, including surgical resection, radiotherapy, chemotherapy and combinations of therapy, but are difficult to compare and assess for efficacy due to the small number of patients and the lack of controlled trials. Reviewing the relevant literature, the patients appeared at their first visit to hospital in various conditions. The backgrounds, such as performance state or stage of disease, of the patients were very different, but we can conclude that the prognosis was better in patients whose condition was good enough to receive some treatment regardless of its method. The patients who received no treatment were all in too poor a condition at the first visit to the hospital.

Surgical resection has been performed in many cases in the past, but although the operated cases were of rather limited disease, their prognoses were extremely poor when treated by operation alone (4–6), and it seemed that the operation encouraged the dissemination of the disease. In several cases the metastatic site was not recognized until the operation (4,5,7).

Chemotherapy and radiotherapy were performed in rather extended cases. From the report of Kelsen et al. (8) of the first case of SCC of the esophagus treated by chemotherapy alone, chemotherapy has been chosen as the first management in recent reports (8–12) when an accurate diagnosis could be obtained before operation. Since the histological and clinical characteristics of SCC of the esophagus are so similar to those of the lung, we recommend that SCC of the esophagus be treated by the same regimen used for SCC of the lung, in which chemotherapy remains the mainstay of its management. Kelsen et al. (8) and Levenson et al. (10) recommended chemotherapy as the first line of management. Beyer et al. (9) proposed that combination chemotherapy may provide the best chance for improvement in survival for esophageal SCC, as with SCC of the lung.

**Table 2.** Prognostic significance through multivariate analysis by Cox’s proportional hazard model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (SD)</th>
<th>$P$ value</th>
<th>Risk ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;63/≥63: 0/1)</td>
<td>0.004 (0.310)</td>
<td>0.756</td>
<td>1.004 (0.978–1.030)</td>
</tr>
<tr>
<td>Sex (male/female: 1/0)</td>
<td>–0.145 (–0.507)</td>
<td>0.612</td>
<td>1.004 (0.495–1.513)</td>
</tr>
<tr>
<td>Operation* (yes/no: 1/0)</td>
<td>–0.999 (–3.776)</td>
<td>0.002</td>
<td>0.419 (0.219–0.618)</td>
</tr>
<tr>
<td>Chemotherapy* (yes/no: 1/0)</td>
<td>–1.184 (–3.979)</td>
<td>&lt;0.001</td>
<td>0.3595 (0.171–0.548)</td>
</tr>
<tr>
<td>Radiotherapy* (yes/no: 1/0)</td>
<td>–0.766 (–2.907)</td>
<td>0.0036</td>
<td>0.529 (0.278–0.779)</td>
</tr>
</tbody>
</table>

*statistically significant
There is still some controversy regarding the role of surgery in the management of SCC of the lung. After the 1969 report from the British Medical Research Council (13), surgical treatment was abandoned. However, it has become clear in recent years that a favorable surgical outcome after induction therapy can be expected in a selected group of patients with limited disease (14–17). Several cases of SCC of the esophagus with limited disease, treated by various adjuvant therapies with surgical resection and which achieved longer survival time, were recently reported (18–20). In these cases, those in which preoperative therapy was performed had a better prognosis than did those with postoperative therapy. Mori et al. (18) reported a patient, treated by preoperative chemoradiotherapy, who survived 33 months. Mimori et al. (19) described the efficacy of preoperative hyperthermochemoradiotherapy with 32 and 33 month survival cases, one of whom was alive with no evidence of disease when reported. Each patient had achieved complete reduction of primary tumors before operation. Thus surgical resection after obtaining a complete reduction of the primary esophageal SCC by chemotherapy may achieve longer survival when there is no evidence of metastasis on further examination. However, it is difficult to evaluate the presence of distant metastasis accurately, and there is a high possibility of occult metastasis at the time of diagnosis in most patients, in accord with the evidence of aggressive lymphatic and blood vessel permeation, as is true in SCC of the lung. An accurate diagnosis of the presence of metastasis is so difficult that short survival in resected cases may be due to metastatic lesions which were not diagnosed before operation (4,5,7).

Radiation therapy is effective, as in SCC of the lung, and is now routinely used with limited disease, but because it is only a local control therapy, radiation alone is not favorable as a first treatment. Recurrent patterns of SCC of the esophagus are different from those of the lung: in SCC of the lung, intrathoratic lesions are common (21,22) while in SCC of the esophagus, the liver or other distant organs are common sites (23,24). In addition, because of the presence of the blood-brain barrier, brain radiotherapy may be applied for the prophylaxis or treatment of cerebral metastasis, but its efficacy is not certain (25).

In recent reports of SCC of the esophagus, the effect of a regimen using CDDP seemed to give a better response. Tanabe et al. (12) reported that of the management regimens with five anti-cancer drugs (CDDP, VP-16, VCR, ADM and CPA), CDDP and VP-16 were especially effective, and that brain radiotherapy should be applied for the prophylaxis of cerebral metastasis. They described a patient treated by chemotherapy alone who died from an esophageal tumor which recurred in the brain. Takiyama et al. (11) suggested that the treatment program should emphasize the use of multi-drug regimens, including use of CDDP, active in SCC of the lung, with or without radiation therapy to the primary lesion, and they also included a case report which described that the lack of CDDP after 3 courses of the regimen was regretted. CDDP plus VP-16 has been used more frequently in recent years.

We report here a patient who received 6 courses of a regimen consisting of CDDP and VP-16, which is commonly used for SCC of the lung, with implantation of the reservoir of a central venous catheter to repeat the regimen of chemotherapy. The patient has achieved nine months of survival with no evidence of recurrence, and intends to continue this regimen until any side effects appear.

In conclusion, with SCC of the esophagus it is almost impossible to get complete healing, and local treatment alone such as operation or radiation is not favorable, so it should be treated by multi-drug chemotherapy including CDDP, with or without radiation as the first line treatment. If the patient’s general status permits, the regimen of chemotherapy should be continued to achieve a longer disease-free survival time.

References


