We describe a case of small-cell carcinoma of the esophagus associated with a paraneoplastic neurological syndrome. Sensorimotor neuropathy had developed 3 years earlier, and neurological symptoms had slowly worsened. Small-cell carcinoma of the esophagus was incidentally diagnosed while investigating the cause of the neurological symptoms. A paraneoplastic neurological syndrome was diagnosed on the basis of cancer and exclusion of other known causes of neurological symptoms. The patient was given combination chemoradiotherapy. There was a complete response to three courses of chemoradiotherapy, with no evidence of disease recurrence 6 years after the diagnosis. There was no progression of paraneoplastic neurological symptoms after the complete response.

Key words: small-cell carcinoma of the esophagus – paraneoplastic neurologic syndrome – chemotherapy – radiation therapy

INTRODUCTION
Small-cell carcinoma of the esophagus is a rare disease, characterized by rapid progression. It is associated with a high incidence of metastatic disease at presentation and a poor overall outcome. The incidence rate of small-cell carcinoma of the esophagus ranges from 0.8% to 2.4% of all esophageal malignancies, with only approximately 230 cases described in the literature since the first report by McKeown in 1952 (1–4). We recently encountered a patient with esophageal small-cell carcinoma associated with a paraneoplastic neurological syndrome who responded to chemoradiotherapy. The patient is alive at the time of this report, 6 years after the diagnosis, and has resumed normal daily activities. A paraneoplastic neurological syndrome was first described in 1948 by Denny-Brown (5). Croft and Wilkinson have reported that paraneoplastic neurological syndromes are extremely rare in patients with cancer, with an estimated incidence of 6.6% (6). To our knowledge, a paraneoplastic neurological syndrome in a patient with small-cell carcinoma of the esophagus has not been reported previously.

CASE REPORT
A 63-year-old woman presented with weakness of the lower extremities and numbness of the hands and feet on 3 February 1999. She had difficulty walking without a cane. The patient was a social drinker and used to smoke one pack of cigarettes per day. She had no abnormal findings on physical examination. However, neurological examination revealed glove and stocking type impairment, severe motor weakness and muscular atrophy in the proximal parts of the arms and legs, and absence of tendon reflexes in the knees and ankles. Laboratory values were within normal limits. Her neurological symptoms had slowly yet progressively worsened. The patient presented with sensory symptoms consistent with a diagnosis of sensory neuropathy and had severe motor weakness, possibly caused by involvement of motor neurons in the anterior horn of the spinal cord or the peripheral nerves. Paraneoplastic neurological syndrome caused by the presence of cancer was diagnosed after exclusion of other known causes of neurological symptoms.

Because paraneoplastic sensorimotor neuropathy is usually associated with small-cell carcinoma of the lung and positive tests for onconeural antibodies, especially anti-Hu antibodies, we checked the antibody titer. The test for onconeural antibody (anti-Hu) was found to be positive. Barium studies and endoscopic examination of the upper gastrointestinal tract...
revealed an irregular ulcerated lesion in the middle portion of the esophagus (Figs 1 and 2a). Histological examination of biopsy specimens showed spindle-shaped cells with scant cytoplasm, granular nuclei and inconspicuous nucleoli (Fig. 3). Small-cell carcinoma was diagnosed.

Primary small-cell carcinoma of the esophagus usually differentiates into squamous epithelium or glandular epithelium and is characterized by multiple small-cell carcinomas, with features of both squamous-cell carcinoma and adenocarcinoma. In our patient, we histopathologically diagnosed a pure small-cell carcinoma, without components of squamous-cell carcinoma or adenocarcinoma. A computed tomography (CT) scan showed an esophageal tumor, with enlarged middle thoracic paraesophageal lymph nodes but no abnormality in the chest or abdominal space. There was no evidence of metastasis to the brain. The diagnosis was a T2N1M0 small-cell carcinoma of the esophagus. Laboratory tests revealed an elevated serum pro-gastrin-releasing peptide (pro-GRP) level (127 pg/ml; normal range <46.0 pg/ml). The serum carcinoembryonic antigen (CEA) and squamous-cell carcinoma antigen levels were within normal limits.

In patients with limited small-cell esophageal cancer, Medgyesy and colleagues reported that surgery with curative intent should be considered part of a multimodality treatment. Many patients in whom limited-stage small-cell esophageal cancer is diagnosed undergo esophagectomy. However, most patients with limited small-cell esophageal carcinoma have early recurrence and extensive metastasis. Micrometastases, which cannot be detected before surgery, are common in such patients (7) and, for small-cell carcinoma of the esophagus, cisplatin is commonly used. However, numbness of the hands and feet in our patient may have been adversely affected by treatment with cisplatin. We therefore used combination therapy with carboplatin and etoposide instead of cisplatin.

Combination chemotherapy with 240 mg/m² carboplatin (CBDCA) given intravenously on day 1, plus 50 mg/m² etoposide (VP-16) given intravenously on days 1–3, was started on 10 May 1999. The patient received a total of three courses. Radiation therapy was given to a total dose of 60 Gy. The primary esophageal tumor disappeared after treatment, and no cancer cells were found on examination of an endoscopic biopsy specimen, indicating complete remission of the primary lesion. Figures 1b and 2b, respectively, show the endoscopic picture and esophagogram of the primary lesion.

Figure 1. The esophagogram before and after treatment. (a) The esophagogram obtained before treatment. A well-demarcated tumor with deep excavation can be seen in the middle of the thoracic esophagus. (b) The esophagogram after chemoradiotherapy, demonstrating disappearance of the tumor.

Figure 2. The endoscopic picture before and after treatment. (a) The endoscopic picture obtained before treatment, showing type 2 advanced esophageal cancer with deep excavation. (b) The endoscopic picture obtained after the chemoradiotherapy, showing only one ulcer scar, with no evidence of tumor.
after treatment. Only an ulcer scar was found, with no residual tumor. The serum pro-GRP level was within the normal range. However, numbness of the hands and feet as well as sensory neuropathy persisted, and the patient required a wheelchair at discharge, although she was using only a cane at admission. Recovery from the neurological syndrome is unlikely in the future because of axonal degeneration. As of the time of writing, the patient has survived for more than 6 years since diagnosis and has resumed normal daily activities, with no further treatment and no evidence of recurrent disease. Neurological symptoms have not progressed further.

**DISCUSSION**

Small-cell carcinoma of the esophagus is a rare disease, characterized by an aggressive course similar to that of small-cell carcinoma of the lung. The incidence of this rare esophageal tumor has been estimated to range from 0.8% to 2.4% of all esophageal malignancies. Casas and colleagues (8) compiled data on 199 patients with small-cell carcinoma of the esophagus and evaluated prognostic factors affecting survival. They estimated that the median survival time for patients with limited disease was 8 months, with a survival probability of 17% at 24 months. The median survival time for patients with extensive disease was 3 months, with a survival probability of 0.01% at 24 months. Beyer and colleagues (9) conducted a literature review of 134 cases of esophageal small-cell carcinoma. They reported a median overall survival time of 5.3 months, with a survival probability of 10% at 24 months.

To date, only a few patients have had complete responses to treatment and prolonged survival (10–12). However, our patient, who received combination chemoradiation therapy, has survived for 6 years after diagnosis, with no further treatment and no evidence of recurrent disease. No standard treatment for small-cell carcinoma of the esophagus has yet been defined owing to the paucity of cases studied and the lack of large studies. Since the histological and clinical characteristics of small-cell carcinoma of the esophagus closely resemble those of small-cell carcinoma of the lung, combined modality therapy is often used (13,14). Our results and those of previous studies suggest that combination chemoradiotherapy with carboplatin and etoposide is effective against esophageal small-cell carcinoma and may improve survival.

Among patients with a paraneoplastic neurological syndrome, anticancer treatment is effective against Lambert–Eaton myasthenic syndrome (LEMS) in approximately 40% of cases. Many case reports have provided evidence that LEMS can be controlled by symptomatic medical treatment with steroids, plasma exchange and administration of high doses of γ-globulin preparation and immunotherapy. However, anticancer drugs are effective in only 19% of patients with sensory neuropathy such as that seen in our patient (15). Symptomatic medical therapy and immunotherapy are also usually ineffective, leading to an extremely poor prognosis. In our patient, neurological symptoms did not worsen for more than 6 years after complete remission, suggesting that they were controlled by anticancer therapy.

Neurologists in Japan participated in a nationwide questionnaire survey about paraneoplastic neurological syndromes to examine the number of cases, clinical features and accompanying malignancies (15). Records were collected for 159 cases. The major clinical variations were as follows: sensory neuropathy (54 cases, 34%); LEMS (45 cases, 28%), including 5 cases associated with subacute cerebellar degeneration; subacute cerebellar degeneration (40 cases, 25%); limbic encephalitis (8 cases, 5%). In terms of the type of carcinoma associated with LEMS, small-cell carcinoma was diagnosed in 79% of cases (92% of which originated in the lung); only one case each of small-cell carcinoma of the adrenal gland and lymph gland was reported. In sensory neuropathy, small-cell carcinoma of the lung was present in 28% of cases, other types of lung cancer in 13%, gastric cancer in 20%, ovarian carcinoma in 7%, breast cancer in 7% and nasopharyngeal carcinoma in 6%. Neither type of paraneoplastic neurological syndrome was associated with small-cell carcinoma of the esophagus. This survey also demonstrated that paraneoplastic neurological syndromes are themselves very rare, estimated to occur in 6.6% of all cases of cancer (6).

In our patient, sensory neuropathy worsened slowly yet progressively over the course of 3 years. Subsequent examination revealed that the patient was positive for onconeural (anti-Hu) antibodies and had small-cell carcinoma of the esophagus. Chalk and colleagues (16) have followed up 21 patients who had sensory neuropathy but no evidence of malignant tumors for 23 years and found that no patient had anti-Hu antibodies. In contrast, small-cell lung cancer developed in 91% of the 67 patients who were positive for anti-Hu antibodies. These results show that patients with neurological symptoms who are positive for anti-Hu antibodies have an increased risk of small-cell lung cancer. In conclusion, the present case demonstrates that neurological symptoms of unknown origin may be caused by a paraneoplastic neurological syndrome.
with underlying malignancy. Since the number of patients with cancer has increased in recent years, early diagnosis and treatment of paraneoplastic neurological syndrome is likely to play an increasingly important role in improving outcome.

References