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PROSPECTIVE STUDY

Phase Ⅱ trial of carboplatin/docetaxel in patients with resected NSCLC

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Abstract

AIM: To investigate the development of a safer chemotherapeutic regimen with better compliance, a total of 67 patients were enrolled as a single arm in a two-stage multi-center phase Ⅱ study.

METHODS: The patients received chemotherapy with carboplatin (CBDCA) with an area under the curve (AUC) of 5, and docetaxel (DTX) at 60 mg/m^2 tri-weekly for three cycles after surgery. The primary endpoint of this study was compliance, while the secondary endpoints were the adverse events (AE) and recurrence-free survival (RFS).

RESULTS: Sixty-one patients were treated in this study arm. The patients were 43 males and 18 females, with a median age of 64.6 years. Fifty-one patients (83.6%) completed all three cycles of therapy. The presence of Grade 3 and 4 neutropenia was noted in 25% and 66% of the patients, respectively. The non-hematological AE were less frequently reported, and no treatment-related death was registered. The two-year RFS and OS rates of the 61 patients were 69.8% and 88.3%, respectively.

CONCLUSION: A tri-weekly schedule of CBDCA and DTX as adjuvant chemotherapy showed a favorable feasibility.

Key words: Non-small cell lung cancer; Adjuvant chemotherapy; Carboplatin; Docetaxel; Treatment compliance; Surgical resection

Core tip: Adjuvant chemotherapy with a tri-weekly schedule of carboplatin and docetaxel was feasible in Japanese non-small cell lung cancer patients. In clinical practice, this regimen represents a potential treatment option that may be superior to other regimens. The main limitation associated with this study is the small number of patients enrolled. Therefore, it is important to employ a reference arm for any future randomized clinical trials evaluating this treatment regimen.

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INTRODUCTION

Lung cancer is one of the deadliest cancers worldwide, with the highest incidence and mortality among all cancers[1]. Many of the patients with non-small cell lung cancer (NSCLC) demonstrate a recurrence of the tumor and die despite undergoing a complete surgical resection[2]. This suggests that occult metastases are often present at the time of surgical intervention[3,4]. Therefore, adjuvant chemotherapy is needed to improve the prognosis of patients[5]. The benefits of adjuvant chemotherapy have been demonstrated using mainly cisplatin (CDDP)-based chemotherapy[6]. However, many problems still remain. For example, CDDP-containing regimens pose unacceptable toxicity, require hydration to prevent renal toxicity, and also add a risk for lung edema with a reduced vascular bed after a lung resection[7]. As a result, these regimens often have low patient compliance. Furthermore, treatment-related deaths sometimes occur with CDDP chemotherapy, even although it might prevent recurrence when given in an adjuvant setting and most of the population who cannot gain a privilege[8,9]. Given the poor compliance, randomized studies have failed to prospectively confirm a statistically significant role for adjuvant chemotherapy for NSCLC patients[10,11].

On the other hand, carboplatin (CBDCA) is more favorable with less toxicity than most of the anticancer drugs for advanced lung cancer. Further, CBDCA was not far behind CDDP in a post-surgical situation[12], although CDDP-based chemotherapy yields a barely significant survival advantage compared with combination chemotherapy consisting of CBDCA plus a second generation agent in patients with advanced NSCLC[13]. In fact, there might be large differences between the outcomes of chemotherapy for patients with advanced NSCLC with a large tumor burden and patients receiving the treatment in the adjuvant setting who are at least macroscopically tumor-free. We previously reported that a bi-weekly schedule of CBDCA combined with paclitaxel (PTX) or gemcitabine also had acceptable toxicity[7,14]. In fact, CBDCA treatment regimens are available for outpatients for a short duration of treatment. However, the compliance in the previous studies was still unsatisfactory.

Docetaxel (DTX) has pharmacological actions similar to its congener, PTX. However, these drugs have pharmacodynamic and pharmacokinetic differences[15]. In fact, DTX is the only agent currently approved for both first- and second-line treatment of advanced NSCLC[16]. Furthermore, DTX is superior to vinca alkaloid-based regimens, the most common treatment used in the adjuvant setting, in terms of the overall survival (OS) and safety for advanced NSCLC patients. DTX-based regimens also improved the patient quality of life compared with vinca alkaloid-based regimens in those with advanced NSCLC[17]. Therefore, CBDCA with DTX may offer an acceptable alternative for patients with advanced NSCLC.

The purpose of this study was to test the completion rate as a primary endpoint and the adverse events (AE) and recurrence-free survival (RFS) as secondary endpoints in patients with stage ⅠB-ⅢA NSCLC receiving tri-weekly CBDCA [area under the curve (AUC) 5] and DTX (60 mg/m^2) in a two-stage multi-institutional study.

MATERIALS AND METHODS

Eligibility criteria

Patients were eligible for the main trial if they fulfilled the following local criteria for a pathological diagnosis of stage ⅠB, Ⅱ or ⅢA NSCLC[18] after a curative operation and mediastinal lymphadenectomy: Age 20-80 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; a leukocyte count of 4000 mm^3 and a neutrophil count of 2000 mm^3 or greater; a hemoglobin level of 9.0 g/dL or greater; a platelet count of 100000 μL or greater; a serum bilirubin level less than 1.5 mg/dL; and aspartate aminotransferase and alanine aminotransferase levels equal to or less than two times the institutional normal and a creatinine concentration less than 1.5 mg/dL. The patients were ineligible if they had a concurrent malignancy, uncontrollable complications, severe postoperative morbidity; previous treatment, including chemotherapy, radiotherapy or immunotherapy; hypersensitivity to therapeutic agents; and the possibility of being pregnant and other conditions such as hepatic inflammation, as judged by the attending physician. This study was registered with University Hospital Medical Information Network-Clinical Trials Registry, available at http://www.umin.ac.jp/ctr/index-j.htm (ID: UMIN000002425).

Pretreatment and follow-up evaluations

Before enrollment, all patients underwent a full history and clinical examination which included the PS, complete blood cell count (CBC), electrolytes, glucose, liver function tests, blood urea and creatinine levels, a urinalysis, electrocardiogram and chest X-rays. Additional imaging investigations were performed if clinically indicated or in order to measure areas of known disease. During the study, all patients were monitored for symptoms of toxicity and underwent regular clinical examinations. Hematological assessments and chest X-rays, and tumor marker studies were performed at least every three and four weeks, respectively.

Treatment schedule and trial design

This was a two-stage multi-institutional prospective study. A dose of 60 mg/m^2 DTX and CBDCA AUC of 5 were given intravenously on days 1 and every three weeks for a maximum of three cycles[19]. The treatment was started

within 10 wk of surgery. Calvert *et al*[20] formula was used to calculate the AUC for CBDCA, whereas the creatinine clearance was determined using the Jelliffe *et al*[21] formula. A short premedication with 20 mg of dexamethasone and a 5-HT3 receptor antagonist was administered intravenously 30 min before the patients received the rest of the DTX. CBDCA and DTX were dissolved in physiological saline or 5% glucose to a volume of 250 mL, and were administered by intravenous drip infusion in 90 min.

CBC were measured before the beginning of each new treatment course. Treatment was delayed for one week if the leukocyte count was less than 3000/μL, the neutrophil count was less than 1500/μL or the platelet count was less than 75000/μL. The patient was withdrawn from the study if these conditions were not resolved within six weeks[22]. The dose of DTX was reduced to 50 mg/m^2 and the dose of CBDCA was reduced to AUC 4 only once through a full course when the neutrophil count was 1000/μL or less, or the platelet count was 25000 μL or less with previous treatment, or if grade 3 non-hematological toxicities occurred. The maximum grade on the National Cancer Institute of Common Toxicity Criteria for AE (Version 3.0) was reported for both the hematological and non-hematological toxic effects. The highest toxicity grade for each patient in all cycles of chemotherapy was used for toxicity analysis. Patients did not receive prophylactic granulocyte colony-stimulating factor (G-CSF) during any cycle. The criteria for removal from the treatment arm were intolerable toxicity or withdrawal of consent. The choice of any subsequent treatment depended on the institution. The Institutional Review Board approved this study and informed consent was obtained from either the patients or their legal guardians.

Observations and evaluations

The primary endpoint of this study was compliance with the chemotherapy protocol, while the secondary endpoints were the AE and RFS. All eligible patients who received any treatment were considered assessable for toxicity. The blood chemistry studies and evaluations of the serum levels of tumor markers were repeated every cycle. The follow-up period after accrual closure was planned to be 24 mo.

Statistical analysis

The expected and threshold values of the treatment completion rate were 80% and 65%, respectively[7,14]. The number of patients required was determined with an α risk of 0.05 and β risk of 0.2. Simon[23] optimal design was applied to recruit the patients and the number of patients required was calculated to be 65 patients by considering the likely number of cases with incomplete treatment. If completion of treatment was observed in < 21 patients among the first 31 patients, this study was to be terminated; if it was observed to be ≥ 22 patients, recruitment would be allowed. The events considered in the RFS were locoregional and distant recurrence. The RFS was calculated from the date of registration to the date of recurrence. The OS was calculated from the date of enrollment to the date of death or last known contact. The terminal event of the overall survival analysis was death attributable to cancer or non-cancer causes. The Kaplan-Meier method was used to estimate the probability of survival and survival differences were analyzed by the log-rank test. The difference was considered to be significant for values of $P < 0.05$. The data were analyzed using the Stat View software program (Abacus Concepts, Inc., Berkeley, California, United States).

RESULTS

Patient characteristics

Sixty-seven patients were enrolled in this multi-institutional trial from September 2009 to August 2011. Thirty-one patients were evaluated at the interim analysis. Completion of treatment was observed in 23 patients among the first 31 patients at the interim analysis[24]. Six of the 67 patients enrolled were excluded from the final analysis; three due to ineligibility criteria and three patients due to not receiving the study treatment. A total of 61 patients were therefore evaluable and their characteristics are shown in Table 1. The 61 patients included 43 males and 18 females, with a median age of 64.6 years (range, 42-79 years). The tumors included 45 adenocarcinomas, 13 squamous cell carcinomas, two pleomorphic carcinomas and one giant cell carcinoma. Nineteen patients were in stage I B, 11 in ⅡA, 10 in ⅡB, and 21 in ⅢA. None of the patients received either induction or postoperative radiotherapy.

Compliance with chemotherapy

The regimen was judged to be safe and tolerable in the first stage and therefore patients were accrued as planned[24]. Fifty-one patients completed all cycles of therapy and therefore, the completion rate was 83.6% (Table 2). The median number of treatment cycles for all patients was three. The primary reason for premature discontinuation was hematological toxicity ($n = 6$). The four patients did not complete all cycles because of a pulmonary fistula in two cases, diarrhea in one case and an intra-abdominal abscess from ileocecal diverticulitis in one case. The transition rate to outpatient status in all cycles was 49.2%. As a consequence of a dose reduction, the mean and median dose intensity of CBDCA were 4.3 (86.7%) and 4.3 (86.7%) AUC and those of DTX were 51.8 mg/m^2 (86.3%) and 53.3 mg/m^2 (88.8%), respectively.

Safety

The toxicity profiles are summarized in Table 3. Grade 3 and 4 neutropenia were observed in 25% and 66% of patients, respectively. Grade three febrile neutropenia developed in 7% of patients, while no grade 4 febrile neutropenia was observed. Severe non-hematological AE were infrequent and no treatment-related death was reg-

Table 1 Patient characteristics

Characteristic	*n* = 61
Gender	
Male	43
Female	18
Age, yr	66 (42-79)
Histology	
Adenocarcinoma	45
Squamous cell carcinoma	13
Pleomorphic carcinoma	2
Giant cell carcinoma	1
Lesion site	
Right	42
Left	19
Lesion location	
Upper	38
Middle	1
Lower	22
Pathological stage (7th)	
ⅠB	17
ⅡA	14
ⅡB	8
ⅢA	22
Surgical procedure	
Sublobar resection	2
Lobectomy	58
Pneumonectomy	1

Table 3 Worst adverse events that occurred in the present study *n* (%)

Toxicity	Grade 3	Grade 4
Hematological events		
Neutropenia	15 (25)	40 (66)
Febrile neutropenia	4 (7)	0 (0)
Non-hematological events		
Anorexia	4[1] (7)	0 (0)
Nausea	2[1] (3)	0 (0)
General fatigue	2 (3)	0 (0)
GI disorder[2]		1 (2)
Diarrhea	1 (2)	

[1]Two patients had both anorexia and nausea; [2]Intra-abdominal abscess from ileocecal diverticulitis. GI: Gastrointestinal.

istered. Peripheral neuropathy (Grade 1) was observed in four (6.6%) of the 61 patients.

Efficacy

There were 20 events (12: Alive with recurrence; 7: Dead with recurrence; 1: Dead without cancer) recorded in the 61 patients. The overall median follow-up period for all patients was 29.9 mo. The two-year RFS and OS rates of the 61 patients were 69.8% and 88.3%, respectively. The two-year RFS rate of the patients with stage ⅠB, Ⅱ and ⅢA tumors was 94.1%, 69.6% and 50.0%, respectively ($P < 0.01$) (Figure 1B). The two-year OS rate in patients with stage ⅠB, Ⅱ and ⅢA tumors was 94.1%, 81.0% and 85.6%, respectively ($P = 0.0282$) (Figure 2B). There was a significant relationship between the pathological stage and the number of recurrences (stage ⅠB-Ⅱ: 17.9%, ⅢA: 59.1%, $P < 0.01$; Table 4).

Table 2 Drug delivery *n* (%)

Number of cycles delivered	
1	61 (100)
2	58 (95)
3	51 (84)
Total	170
Median	3
Number of patients who required dose reduction of	
CBDCA	43 (70)
DTX	43 (70)
Mean dose intensity (% planned)	
CBDCA	4.3 AUC (86.7)
DTX	51.8 mg/m^2 (86.3)
Median dose intensity (% planned)	
CBDCA	4.3 AUC (86.7)
DTX	53.3 mg/m^2 (88.8)

CBDCA: Carboplatin; DTX: Docetaxel; AUC: Area under the curve.

Table 4 The pathological stages and types of recurrence *n* (%)

Pathological stage (7th)	No. of cases	Local	Systemic
ⅠB	17	0	1
ⅡA	14	2	2
ⅡB	8	0	3
ⅢA	22	7	10
Total	61	9 (15)	16 (26)

Five patients had both local and systemic recurrent tumors.

DISCUSSION

The medicinal value of an agent increases when an adequate amount of anticancer drug is given. In fact, an average relative dose intensity less than the median predicted a poor prognosis in diffuse large cell lymphoma[25], and in the patients who received at least 85 percent of the planned dose, the rate of RFS was longer than the group that received less than the optimal dose in breast cancer patients[26]. Furthermore, Neymark *et al*[27] reported that the patients' adherence to protocol therapy was linked to a favorable survival in NSCLC.

Of interest, studies addressing the role of preoperative chemotherapy have found chemotherapy compliance to be more favorable in the preoperative setting than for adjuvant treatment. In fact, the compliance/median disease free survival for the preoperative and postoperative groups were 93%/32 and 65%/24 mo[28]. However, the successful delivery of CDDP-based chemotherapy in postoperative patents has been difficult, as described above. At present, the compliance has been unsatisfactory, with rates of 56%-74%, except for cancer and leukemia group B 9633[11,29-31]. Our results showed 83.6% compliance. Recently, Kubota *et al*[32] reported 93% compliance in patients treated in the CDDP + DTX arm who completed 3 planned cycles of chemotherapy. Yang *et al*[33] also reported 85% compliance in patients treated with CBDCA (AUC 5) and DTX (75 mg/m^2), which was consistent with our data.

The presence of severe toxicities, specifically neu-

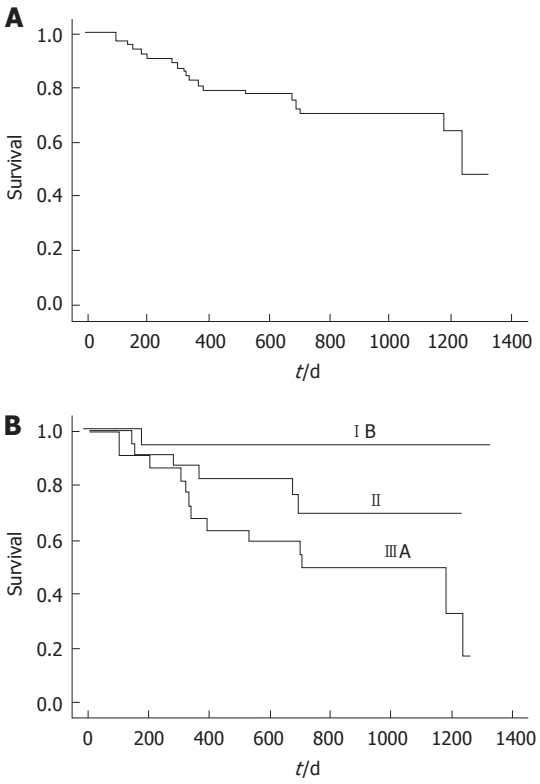

Figure 1 Recurrence-free survival. A: The 2-year recurrence-free survival (RFS) rate was 69.8%; B: The RFS curves stratified by pathological stage.

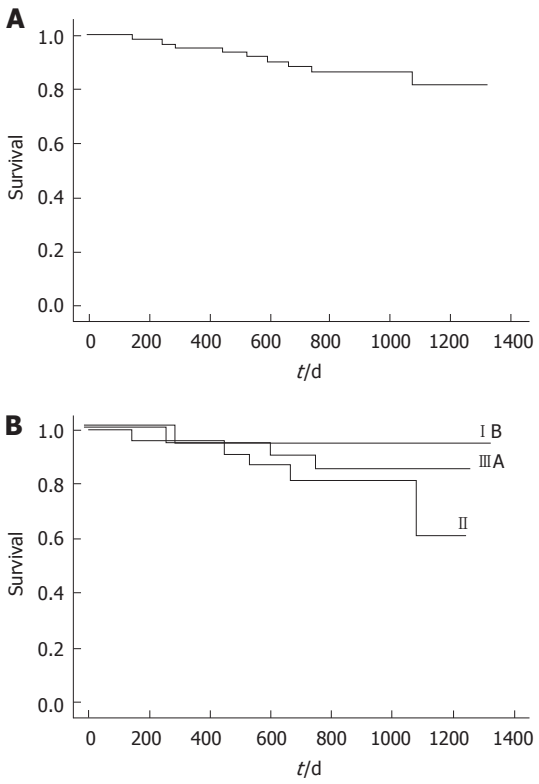

Figure 2 Overall survival. A: The 2-year overall survival (OS) rate was 88.3%; B: The OS curves stratified by pathological stage.

tropenia, was relatively high in our study. The incidence of grade 3/4 neutropenia and grade 3/4 febrile neutropenia was reported to be 86% and 10% for CDDP with DTX for the Japanese patients with completely resected NSCLC, respectively[32]. The frequency of grade 3/4 neutropenia in Japanese patients is much higher than that in Caucasian patients treated with the same tri-weekly schedule[31,34]. The difference in the complication rates might depend on ethnic differences in the population-related pharmacogenomics[35]. Of note, the frequency of severe neutropenia also varies among Japanese and Chinese patients[33]. Therefore, the optimal doses in this combination and the appropriate application of G-CSF should also be considered in a future study. Although the treatment was associated with higher toxicity, it was also associated with good compliance, and our results using DTX-based regimens therefore show that they represent new a therapeutic option[32,36].

The two-year RFS and OS rates of the 61 patients were 69.8% and 88.3%, respectively, in our study. These data were superior to the data in the Japanese lung cancer registry study of 11663 surgical cases, although the data regarding survival are still preliminary and must be followed up[37]. Furthermore, the non-hematological adverse effects were less frequent and no treatment-related death was registered in this trial. However, patients with advanced stage NSCLC had a significantly poorer prognosis in terms of the RFS, although there were no statistically significant differences between stage I B-II and III patients in terms of the OS. Therefore, the selection of regimens with sufficient efficacy for restricting the growth of a recurrence might be needed. Recently, a Japan Intergroup Trial phase III trial of pemetrexed as adjuvant chemotherapy for completely resected non-squamous cell carcinoma has been launched. In the present study, we demonstrated the feasibility of DTX combined with CBDCA; therefore, the next step would be to compare this regimen to CDDP with new drug(s) in a phase III trial.

In conclusion, adjuvant chemotherapy with a tri-weekly schedule of CBDCA and DTX was feasible in Japanese NSCLC patients. In clinical practice, this regimen represents a potential treatment option that may be superior to other regimens. The main limitation of this study is the small number of patients enrolled and therefore it is important to employ a reference arm for any upcoming randomized clinical trials evaluating this treatment regimen.

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COMMENTS

Background

The benefits of adjuvant chemotherapy have been demonstrated for patients with non-small cell lung cancer (NSCLC). However, some problems still remain

and treatment-related deaths sometimes occur. Therefore, the development of a safer regimen with better compliance is still necessary.

Innovations and breakthroughs

The present results suggest that adjuvant chemotherapy with a tri-weekly schedule of carboplatin and docetaxel is feasible in Japanese NSCLC patients.

Applications

In clinical practice, this regimen represents a potential treatment option that may be superior to other regimens.

Peer review

This is an informative and very well-written manuscript which is useful for interested readers and investigators of lung cancer.

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CASE REPORT

Solitary pituitary metastasis resulting from pulmonary large cell neuroendocrine carcinoma

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Abstract

Solitary pituitary metastasis is a rare phenomenon in human neoplasms. We report a case of lung cancer with the initial manifestation of endocrinopathy resulting from pituitary metastasis. The patient's initial diagnosis was a poorly differentiated carcinoma, however, morbid anatomy revealed a definite diagnosis of large cell neuroendocrine carcinoma (LCNEC). Clinical physicians should be aware of potential initial manifestations such as endocrine abnormalities including panhypopituitarism and diabetes insipidus due to solitary pituitary metastasis. This case demonstrates that an endocrine abnormality such as panhypopituitarism could be an initial manifestation of LCNEC.

Key words: Large cell neuroendocrine carcinoma; Pituitary metastasis; Solitary; Endocrinopathy

Core tip: Solitary pituitary metastasis is a rare phenomenon in human neoplasms. An endocrine abnormality such as panhypopituitarism could be an initial manifestation of large cell neuroendocrine carcinoma.

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INTRODUCTION

Pulmonary neuroendocrine tumors consist of typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). LCNEC is an uncommon malignancy with aggressive features and a dismal prognosis. Although brain metastasis is often observed in patients with LCNEC, to our knowledge, there is no description of solitary pituitary metastasis due to LCNEC. Here, we describe a case of LCNEC with the initial manifestation of endocrinopathy secondary to pituitary metastasis.

CASE REPORT

A 74-year-old man with a smoking history presented with anorexia, vomiting, fever and thirst. Physical examination revealed dry mouth, decreased skin turgor and hypotonia with a blood pressure of 80/50 mmHg. Laboratory investigations revealed thyroid stimulatory hormone of 0.05 U/mL [normal range (NR): 0.5-5.5 U/mL], luteal hormone

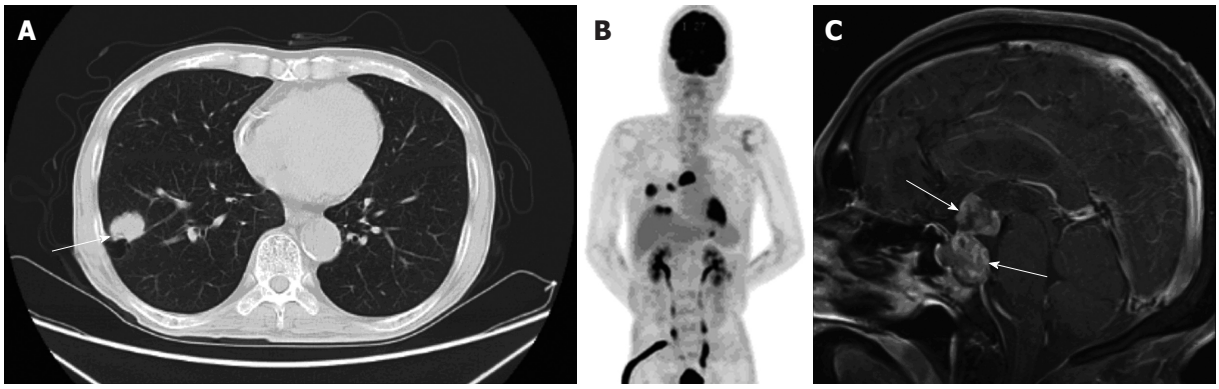

Figure 1 A 74-year-old man with a smoking history presented with anorexia, vomiting, fever and thirst. A: Chest computed tomography reveals a mass on the right upper lobe (white arrow); B: Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography image shows FDG accumulation at the primary site, hilar and mediastinal lymph nodes, and liver; C: Sagittal view of gadolinium-enhanced brain magnetic resonance imaging shows irregularly enhanced dumbbell-shaped tumor in the intrasellar and suprasellar areas (white arrows).

< 0.07 IU/mL, follicle stimulating hormone of 0.6 mIU/mL, testosterone of 2.51 ng/mL (NR: 1.31-8.71 ng/mL), growth hormone of 1.00 ng/mL, insulin-like growth factor 1 of 11.0 ng/mL (NR: 121-436 ng/mL), adrenocorticotropic hormone of 2.4 pg/mL (NR: 1.0-5.2 pg/mL), and urinary free cortisol < 0.5 μg/d (NR: 11.2-80.3 μg/d), suggesting panhypopituitarism including secondary adrenal failure. The patient had symptoms of thirst, polyposia and increased urination (over 3 L/d). Laboratory investigations revealed low urine specific gravity of 1.004, plasma osmolarity of 319 mOSM, low urine osmolarity of 194 mOSM (< 300 mOSM/kg), and the ratio was 0.686 (< 1). The administration of 1-desamino-8-*D*-arginine vasopressin resulted in urine volume reduction and urine condensation. A definite diagnosis of diabetes insipidus was made following these laboratory investigations and physical examination.

Computed tomography of the chest showed a mass on the right upper lobe and swelling of mediastinal lymph nodes (Figure 1A). Percutaneous needle biopsy diagnosed a poorly differentiated adenocarcinoma. Brain magnetic resonance imaging showed a dumbbell-shaped gadolinium-enhanced tumor in the pituitary (Figure 1B). 2-^{18}F-fluoro-2-deoxy-*D*-glucose (^{18}F-FDG) positron emission tomography (PET) revealed an increased accumulation of ^{18}F-FDG in the lung, pituitary, liver and mediastinal lymph nodes (Figure 1C). A definite diagnosis of primary lung cancer stage Ⅳ (cT1bN2M1b) was made. However, the patient had pan hypopituitary symptoms with a performance status of 4. Therefore, palliative radiation therapy was administered for the solitary pituitary mass in order to improve the patient's quality of life. Following radiotherapy of 50 Gy/25 fr, the patient experienced an improvement in appetite and nausea. On the 58th hospital day, the patient was discharged from our institution due to improving quality of life. However, he died as a result of severe pneumonia and disseminated intravascular clotting due to progression of the primary disease 10 d after discharge. Evaluation of morbid anatomy was performed following permission from the bereaved family. The immunohistochemical findings of primary lung tumor and solitary pituitary metastasis revealed marked positive staining of chromogranin A, CD56 (NCAM) and synaptophysin. The final diagnosis was solitary pituitary metastasis resulting from LCNEC.

DISCUSSION

Postmortem studies have shown that pituitary gland metastasis is observed in 0.14% to 28.1% of all brain metastases and patients with breast and lung cancer account for approximately two thirds of these metastases[1]. Although solitary pituitary metastasis is an extremely rare condition, the histology of adenocarcinoma or small-cell carcinoma is often seen in patients with lung cancer[2]. In our patient, the diagnosis was poorly differentiated adenocarcinoma by percutaneous needle biopsy, however, a definite diagnosis of LCNEC was subsequently made. The diagnosis of LCNEC is difficult to establish based on small biopsies or cytology, because there is a limit to evaluating a neuroendocrine pattern morphologically[3]. Recently, Shimada *et al*[4] proposed the term "high-grade neuroendocrine carcinoma-probable LCNEC (HG-pLCNEC)" from biopsy findings and aimed to elucidate the clinical features compared with SCLC, suggesting that therapeutic efficacy in HG-pLCNEC is similar to that of SCLC. The diagnostic criteria of LCNEC are problematic in biopsy specimens, and our patient was initially diagnosed with poorly differentiated adenocarcinoma.

The patient developed the primary symptom of panhypopituitarism due to pituitary metastasis. Radiologically, it is important to differentiate between pituitary metastasis derived from primary lung cancer and pituitary carcinoma. As primary pituitary carcinoma has an occurrence of 0.1%[5,6], its definite diagnosis requires pathological evidence of a pituitary mass. In our case, the pituitary mass was not treated surgically due to the patient's poor performance status.

A retrospective study demonstrated that 10 of 1639 lung cancer patients (0.61%) had the initial manifestation of central diabetes insipidus[7]. Panhypopituitarism due to solitary pituitary metastasis is relatively rare, therefore,

may be overlooked as an initial symptom of lung cancer. Although multiple brain metastases due to LCNEC are a frequent occurrence, a single pituitary metastasis may also occur. These symptoms can be masked by systemic complications of malignancy, including nonspecific symptoms (malaise, weakness, vomiting, weight loss) and central nervous system involvement. There may be a number of patients with primary cancer whose pituitary insufficiency is not appropriately diagnosed. The possibility that lung cancer has metastasized to the pituitary gland should be considered, and the administration of appropriate endocrine replacement in a timely manner can improve symptoms due to these lesions.

Clinical physicians should be aware of potential initial manifestations such as endocrine abnormalities including panhypopituitarism and diabetes insipidus due to solitary pituitary metastasis.

COMMENTS

Case characteristics

A 74-year-old man with a smoking history presented with anorexia, vomiting, fever and thirst.

Clinical diagnosis

The diagnostic criteria of large cell neuroendocrine carcinoma (LCNEC) are problematic in biopsy specimens, and the present case was initially diagnosed with poorly differentiated adenocarcinoma.

Differential diagnosis

Panhypopituitarism due to solitary pituitary metastasis is relatively rare, therefore may be overlooked as an initial symptom of lung cancer.

Treatment

Clinical physicians should be aware of potential initial manifestations such as endocrine abnormalities including panhypopituitarism and diabetes insipidus due to solitary pituitary metastasis.

Experiences and lessons

This case demonstrates that an endocrine abnormality such as panhypopituitarism could be an initial manifestation of LCNEC.

Peer review

The pituitary metastasis of LCNEC is a very rare condition and the message derived from the case is clinically useful.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases.

Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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