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Case report

A case of *ALK*-rearranged lung adenocarcinoma associated with syndrome of inappropriate antidiuretic hormoneYoshihiro Miyashita^{a,*}, Kotaro Hanawa^a, Hiroaki Kobayashi^a, Takashi Kumagai^a, Kie Inomata^a, Toshiharu Tsutsui^a, Yumiko Kakizaki^a, Toshio Oyama^b^a Department of Pulmonary Medicine, Yamanashi Prefectural Central Hospital, Japan^b Department of Pathology, Yamanashi Prefectural Central Hospital, Japan

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ABSTRACT

A 60-year-old man with a history of smoking was transferred to our hospital for consciousness disorder. A diagnosis of *ALK*-rearranged lung adenocarcinoma associated with a paraneoplastic electrolytic disorder was made following a cutaneous needle biopsy. Both the primary lung lesion and multiple metastases shrunk and his electrolytic disorder resolved after the introduction of a first-line molecular-targeted drug chemotherapy with crizotinib. We herein report a case of *ALK*-rearranged lung adenocarcinoma accompanied by SIADH, successfully treated with crizotinib.

1. Introduction

ALK gene rearrangements are found in approximately 3.4%–6.2% of resected non-small cell lung cancer (NSCLC) cases [1,2]. Since *ALK* rearrangement has been identified as a driver oncogene in NSCLC [3], molecular-targeted therapy for NSCLC harboring the *ALK* rearrangement has progressed.

Paraneoplastic syndromes occur in at least 10% of patients with bronchogenic carcinoma [4]. A larger series of patients has revealed that SIADH occurs in 0.7% of patients with NSCLC (three cases out of 427 patients) [5]. SIADH in *ALK*-rearranged NSCLC has not been previously reported. We herein report a case of *ALK*-rearranged lung adenocarcinoma accompanied by SIADH, successfully treated with crizotinib.

2. Case report

A 60-year-old man was transferred to our hospital in August 2014 due to a consciousness disorder. He had no remarkable medical history but for a 20 pack-year smoking history. Physical examination indicated a grossly distended sternum and several palpable lymph nodes at the left axial fossa. Laboratory data revealed severe hyponatremia combined with hypertonic sodium diuresis. His renal and adrenal functions were normal, and the serum levels of ADH, NT-proBNP, and several tumor markers were slightly elevated (Table 1). Contrast-enhanced chest computed tomography (CT) revealed a giant mass lesion in the left lower

lung field and multiple bone metastases (Fig. 1A and B). Abdominal CT revealed bilateral adrenal gland metastases and peritoneal tumor dis-seminations (Fig. 1C and D).

Transcutaneous needle biopsy was performed at the sternum. A diagnosis of poorly differentiated adenocarcinoma was made according to the pathological findings (Fig. 2), and immunohistochemical analysis showed positive staining for *ALK* (Fig. 3). An additional fluorescence in-situ hybridization (FISH) test confirmed the diagnosis of *ALK* gene rearrangement in lung adenocarcinoma (data not shown). The patient's electrolytic disorder was compatible with SIADH according to a systemic screening examination.

Post-diagnosis, an electrolytic replacement therapy with administration of the first-line molecular-targeted drug crizotinib was significantly effective, and the serum Na concentration recovered from 98.7mEq/L to 130mEq/l. A shrinkage in both the primary lung lesion and multiple metastases was observed upon resolution of the electrolytic disorder (Fig. 4). Other than an ileus induced by abdominal tumor shrinkage, no adverse reactions to chemotherapy were observed. The complete response was maintained with crizotinib for one year without recurrence of the tumor and SIADH. His tumor relapsed at the right upper arm bone and cervical lymph nodes, and alectinib was introduced as second line treatment after radiation therapy for pain control of the right upper arm bone. A partial response was observed, and SIADH did not relapse until the end of his life, on July 2017.

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Table 1
The patient's Laboratory Findings on Admission.

【Hematology】		【Tumor markers】	
White blood cells	18700/ μ L	CEA	39.5 ng/mL
Red blood cells	556 104/ μ L	CA19-9	70.5 U/mL
Hemoglobin	14.6/dL	SCC	81.7 ng/mL
Hematocrit	44.90%	SLX	130 U/mL
Platelets	504 104/ μ L	NSE	59.3 ng/mL
		pro-GRP	59.4 ng/mL
【Blood chemistry】		【Urinalysis】	
Total protein	7.0g/dL	Specific gravity	1.041
Albumin	3.6g/dL	Proteinuria	+
Blood urea nitrogen	11.8mg/dL	Hematuria	2+
Creatinine	0.71mg/dL	Red blood cells	5-9/HPF
Sodium	98.7mEq/L	White blood cells	1-4/HPF
Potassium	5.7mEq/L	Urinary-Na	50.7 mEq/L
Chloride	67.2mEq/L	Urinary-K	40.9 mEq/L
C-reactive protein	22.9mg/dL	Urinary-Cl	51.0 mEq/L
NT-proBNP	3089pg/mL	Urine osmotic pressure	550.0mOsm/L
Serum osmotic pressure	217.0mOsm/L		
Antidiuretic hormon	3.6pg/mL		
Cortisol	21.2 μ g/dL		

CEA:carcinoembryonic antigen.

CA19-9:carbohydrate antigen 19-9.

SCC:squamous cell carcinoma antigen.

SLX:sialy lex-I antigen.

NSE:neuron-specific enolase.

pro-GRP:pro-gastrin releasing polypeptide.

3. Discussion

ALK gene rearrangements are found in approximately 3.4%–6.2% of resected NSCLC cases [1,2]. Crizotinib is one of the most widely available drugs, and is an oral small-molecule tyrosine kinase inhibitor that targets ALK, MET, and ROS1 tyrosine kinases [6]. Crizotinib has been approved in Japan (since March, 2012) and the USA (since August 2011) in any line of treatment, and alectinib was also approved in the first-line setting since 2017 [7].

Paraneoplastic syndromes occur in at least 10% of patients with bronchogenic carcinoma [4]. A larger series of patients has revealed that SIADH occurs in 15% of small cell lung cancers (SCLC) (214 of 1,473 patients), and in 0.7% of patients with NSCLC (three of 427 patients) [5]. A review of clinical data from 350 patients with SCLC revealed that hyponatremia (sodium concentration < 130 mEq/L) was attributed to SIADH in 11% of the patients, and there was no correlation between the development of SIADH and factors such as sex, histologic subtype, clinical stage, and distribution of metastatic sites [4]. All patients with hyponatremia related to SIADH in lung cancer have elevated serum levels of ADH; however, atrial natriuretic peptide is another hormone produced ectopically by lung cancer cells, which affects renal salt and water handling [5]. Hyponatremia in SCLC was significantly associated with a shorter survival duration of the study cohorts in seven of the 13 studies on univariate analysis (54%), and in six studies on multivariate analysis (46%) [9]. However, another study reported that hyponatremia in SCLC was prognostic for a shorter survival time in patients with extensive disease but not in patients with limited disease in a Japanese cohort [10]. The potential life-threatening hyponatremia (sodium concentration less than 100 mEq/L) in the present case might have occurred due to a large tumor burden accompanied by multiple metastatic sites and a large primary pulmonary tumor, in conjunction with elevated serum ADH and NT-proBNP concentrations. We successfully treated life-threatening hyponatremia by electrolytic replacement therapy for the acute symptomatic phase followed by crizotinib, a drug against the molecular target. Despite initial control of SIADH, dilutional hyponatremia recurred in 70% of patients, with tumor regression in SCLC patients [8]. In the present case, hyponatremia did not recur during the administration of crizotinib or at the time of disease progression. However, careful attention should be paid to the recurrence of SIADH in the treatment duration.

4. Conclusion

To the best of our knowledge, SIADH in ALK-rearranged NSCLC has not been reported. Clinicians should be aware that hyponatremia

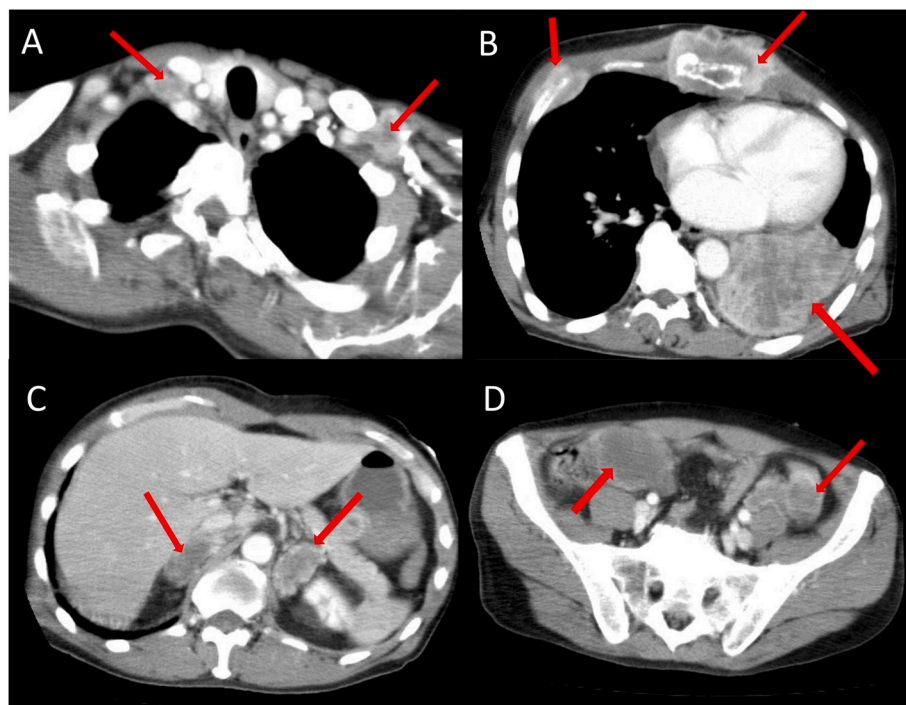


Fig. 1. Chest CT showed a tumor mass measuring 90 × 80 mm in the left lower lung with metastasis to the sternum, right rib, and both supraclavicular lymph nodes (A, B; arrows). Abdominal CT showed metastatic bilateral adrenal glands and peritoneal lesions (C, D; arrows).

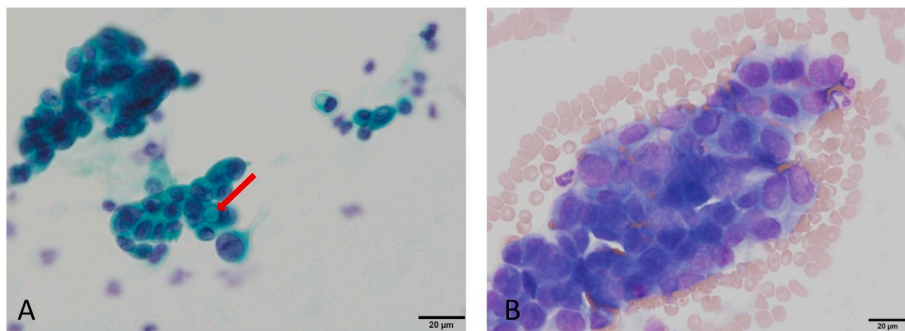


Fig. 2. A cytological specimen obtained by a transcutaneous needle biopsy at the sternum showed atypical epithelial cells with eccentric nuclei and intracytoplasmic (ICL) cells (arrow), which led to the diagnosis of adenocarcinoma (A: Papanicolaou staining, original magnification $\times 200$, B: Giemsa staining, original magnification $\times 200$).

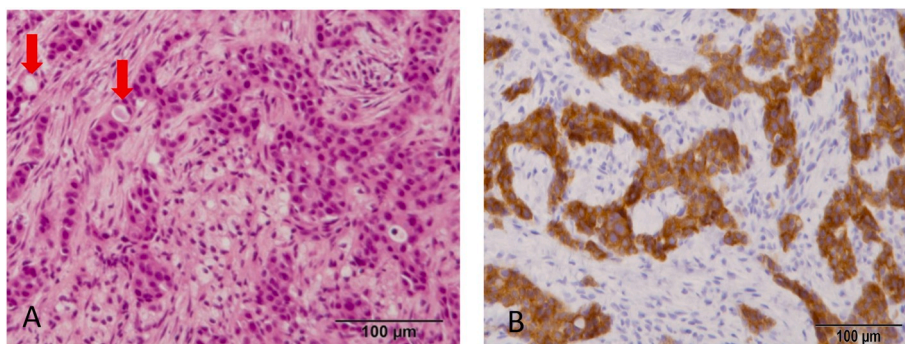


Fig. 3. A pathological specimen obtained by a transcutaneous needle biopsy at the sternum showed atypical cell clusters in the desmoplastic stroma (A: hematoxylin and eosin staining, original magnification $\times 400$). These atypical cell clusters showed trabecular and solid structures with small glands (arrows). Immunohistochemical staining for ALK was positive (B, original magnification $\times 400$).

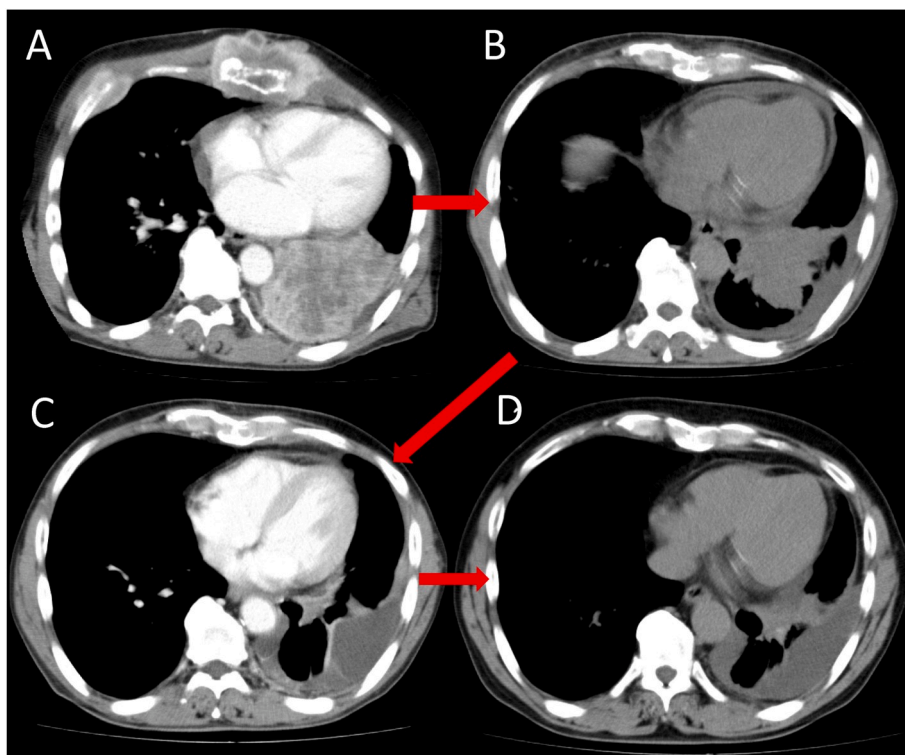


Fig. 4. The primary lung tumor markedly shrunk after the introduction of chemotherapy as demonstrated on serial CT images; on admission (A), 10 days after the introduction of chemotherapy (B), 70 days (C), and 140 days (D).

complicated with lung cancer may be caused by ALK-rearranged NSCLC as well as small cell lung cancer.

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Declaration of competing interest

The authors state that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101136>.

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