Spontaneous regression of small cell lung cancer combined with cancer associated retinopathy

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20 **Abbreviations:** CAR = cancer associated retinopathy; CTL = cytotoxic T
21 lymphocyte; EBUS-TBNA = endobronchial ultrasound-guided
22 transbronchial needle aspiration; ERG = electroretinogram; SR =
23 spontaneous regression; SCLC = small cell lung cancer

24 **Key Words:** Small cell lung cancer, Cancer associated retinpathy,
25 Spontaneous regoression, Recoverin

Abstract

Spontaneous regression (SR) is defined as the complete or partial disappearance of disease without anticancer treatments. We report a case of SR of small cell lung cancer (SCLC) combined with cancer associated retinopathy (CAR). A 65-year-old woman was admitted to our hospital to examine abnormal shadows of the lung with visual loss. She was diagnosed with SCLC associated with CAR. Subsequent chest X-ray and CT scan showed partial regression of both primary tumor and lymph node metastasis without anticancer treatment. Recoverin antigen was present on the tumor cells and anti-recoverin antibody was observed in the patient's serum. Activation of recoverin-specific antitumor cytotoxic T lymphocyte (CTL) was observed in this patient. SCLC was considered to reduce spontaneously by the activation of recoverin-specific antitumor CTL. To the best of our knowledge, this is the first report of SR in SCLC combined with CAR.

1 . INTRODUCTION

Small cell lung cancer (SCLC) accounts for 20% of lung cancers [1] and often leads to paraneoplastic syndrome, which is a remote effect on various organs without direct invasion or metastasis of tumor cells. Cancer associated retinopathy (CAR) is a rare paraneoplastic syndrome that is usually associated with SCLC [2]. Patients with CAR typically present with photosensitivity, ring scotoma, and attenuated retinal arteriole along with undetectable signals on an electroretinogram (ERG) [3]. The autoantibodies that react with photoreceptor proteins, including recoverin, might induce degeneration of photoreceptors and result in poor visual prognosis in patients with CAR [4]. It was reported that recoverin was expressed in tumor tissues in 68% of patients with SCLC and anti-recoverin antibodies were found in sera in 15% of those patients, respectively. However, none of these patients developed CAR [5].

Spontaneous regression (SR) is defined as the complete or partial disappearance of disease without effective anticancer treatments, continuing for 1 month. Although SR occurs in many types of cancers, it is rare, especially in SCLC [6, 7]. Here, we report a case of SR of SCLC combined

58 with CAR in a 65-year-old woman.

59

60 ## 2. CASE REPORT

61 A 65-year-old woman with an existing smoking history of 35 pack-years was
62 admitted to our hospital for evaluation of a right upper nodule revealed on a
63 chest X-ray film (Fig. 1A). Chest computed tomography (CT) scan revealed a
64 primary tumor in the right upper lobe with right supraclavicular and
65 mediastinal lymph node swelling (Fig. 1B, C, D). Laboratory examination
66 showed elevated levels of gastrin-releasing peptide precursor (pro-GRP) and
67 neuron-specific enolase (NSE), at 115.0 pg/ml (normal range less than 80.9
68 pg/ml) and 15.5 ng/ml (less than 12.0 ng/ml), respectively. Tumor specimens
69 of the right lower paratracheal lymph node obtained by endobronchial
70 ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were
71 positive for neuroendocrine makers including CD56, chromogranin A and
72 synaptophysin and confirmed the histological diagnosis of SCLC (Fig.2A).

73 The patient complained of blurred vision in both eyes 11 days after
74 admission. Her best-corrected visual acuity was finger counting in the right
75 eye and 0.1 in the left eye. Although funduscopic examination showed the

appearance of both eyes to be normal, Goldmann perimetry showed a large central scotoma in the right eye and a ring scotoma in the left eye. ERG showed poor responses in both eyes. Recoverin antigen was present in the lung cancer cells and anti-recoverin antibody was observed with high titer (1:2000) in the patient's serum (Fig. 2B, 3). Finally, she was diagnosed with limited disease of SCLC (cT1bN3M0 stageⅢB) associated with CAR. After diagnosis of SCLC, chest X-ray and CT scan prior to anticancer treatment revealed the SCLC to have partially regressed. Furthermore, levels of both pro-GRP and NSE had already decreased before EBUS-TBNA examination, and decreased further to normal range. *In vitro,* IFN-γ ELISPOT assay was performed, using recoverin peptide to stimulate peripheral blood mononuclear cells taken from the patient. The number of CD8+ T cells secreting IFN-γ that reacted to R64 peptide (recoverin-derived HLA-A24 restricted peptide R64) was significantly larger than that of T cells without peptide in the patient (Fig. 4 A, B).

The patient was treated with chemotherapy comprising cisplatin (80 mg/m^2) on day 1 and etoposide (100 mg/m^2) on days 1, 2, and 3. In addition, oral prednisolone (40 mg daily) was initiated for CAR and gradually tapered

over 6 months.

When four courses of chemotherapy had been completed, the primary tumor and lymph-node metastasis had reduced and a good partial response was achieved. Furthermore, her visual acuity had markedly improved, to 0.6 in the right eye and 1.0 in the left eye with amelioration of the visual field defects.

3. DISCUSSION

In this case, reduction of SCLC occurred prior to any anticancer treatment. SR of malignancy has been reported in almost all types of human cancer, but is rare in SCLC with only six previous cases having been reported [8-13]. All previous cases were associated with paraneoplastic sensory neuronopathy, which is caused by anti-neuronal antibodies such as anti-Hu. To the best of our knowledge, this is the first report of SR in SCLC combined with CAR.

Although the reasons for SR remain unclear, a possible hypothesis would be induction of tumor immunologic reaction. Maeda *et al.* have reported that the recoverin-specific cytotoxic T lymphocyte (CTL) was induced in the peripheral blood of cancer patients with CAR and caused tumor cell

112 regression in experimental mouse-model-grafted recoverin-expressing
113 tumor cells [14]. In our patient, activation of recoverin-specific antitumor
114 CTL for R64 peptide was observed. Thus, antitumor immunity against
115 recoverin might have resulted in SR in this case.

116 In conclusion, this is the first report of SR in SCLC combined with CAR.
117 SCLC was considered to reduce spontaneously by immune response induced
118 by recoverin. In addition, immediate diagnosis and anticancer therapy is
119 valuable not only for decreasing tumor burden but also for recovering visual
120 disorder in SCLC combined with CAR.

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122 **Conflicts of interest statement:** None declared.

123 **Source of funding**: None declared.

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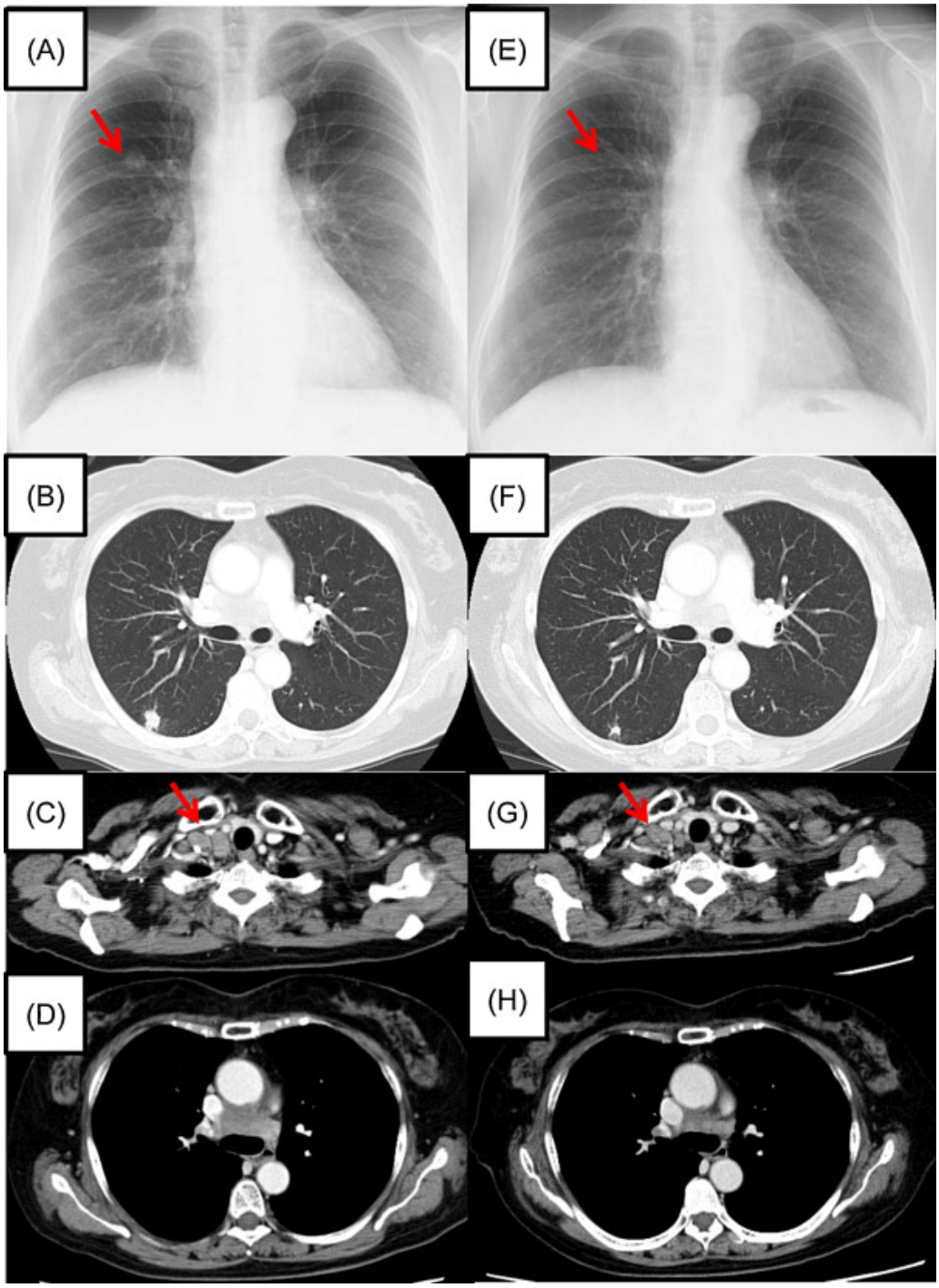
Fig. 1.

Chest X-ray and CT show spontaneous regression of primary tumor and lymph node metastasis in the present case. (A) Right upper mass (arrow) in first examination. (B) Primary tumor in the right S2 in first examination. (C) Right supraclavicular lymph-node metastasis (arrow) in first examination. (D) Mediastinal lymph node metastasis in first examination. (E) Partial spontaneous regression of the right upper mass, subsequent chest X-ray. (F) The primary tumor, (G) right supraclavicular lymph node and (H) mediastinal lymph node decreased, subsequent CT.

125

Fig. 1



126

Fig. 2.

Microscopic appearance of tumor biopsy specimen. (A) Hematoxylin-eosin staining shows small-cell carcinoma cell pattern (original magnification, 100×, 400×). (B) The presence of recoverin antigen on the tumor cells was verified by immunohistochemistry (original magnification, 400×). Positive control: small cell carcinoma (SBC1) tumors established in xenograft mouse models. Negative control: adenocarcinoma and human normal lung.

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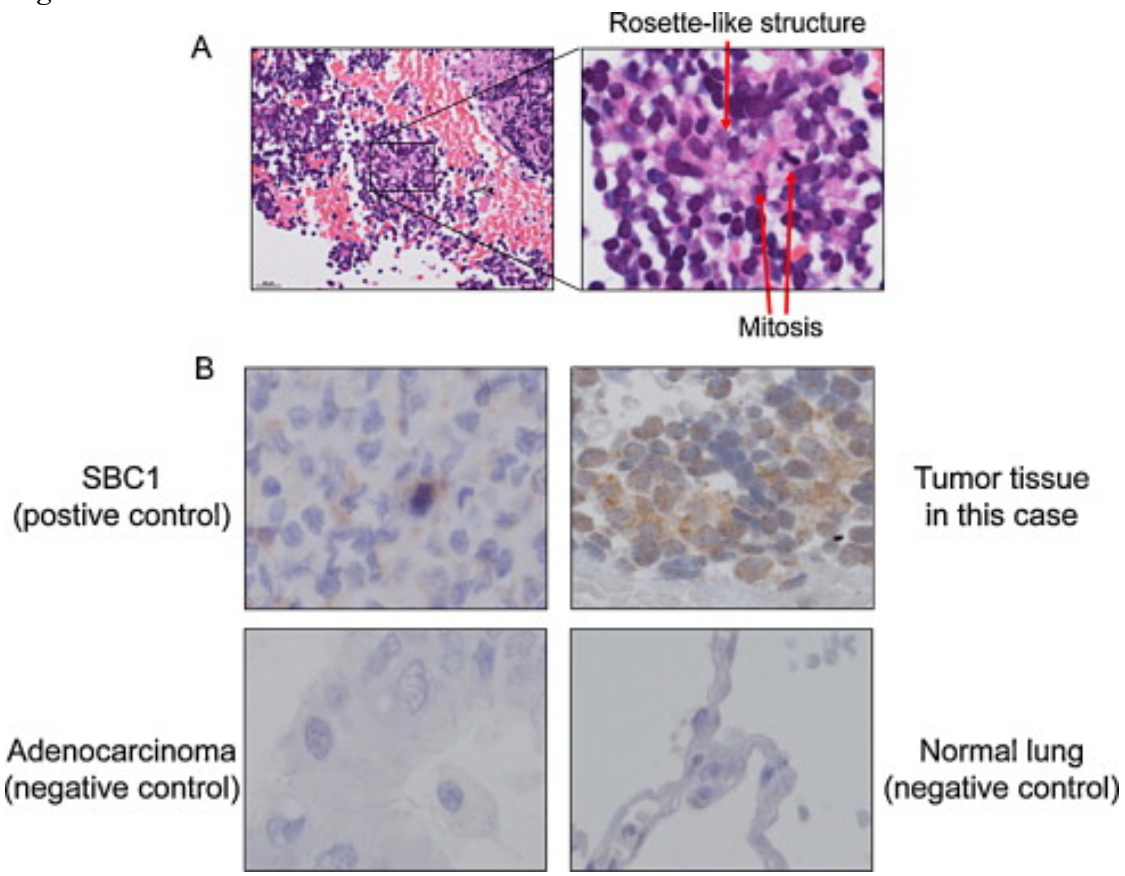
128 Fig. 2


A
Rosette-like structure
Mitosis
B
SBC1
(postive control)
Tumor tissue
in this case
Adenocarcinoma
(negative control)
Normal lung
(negative control)

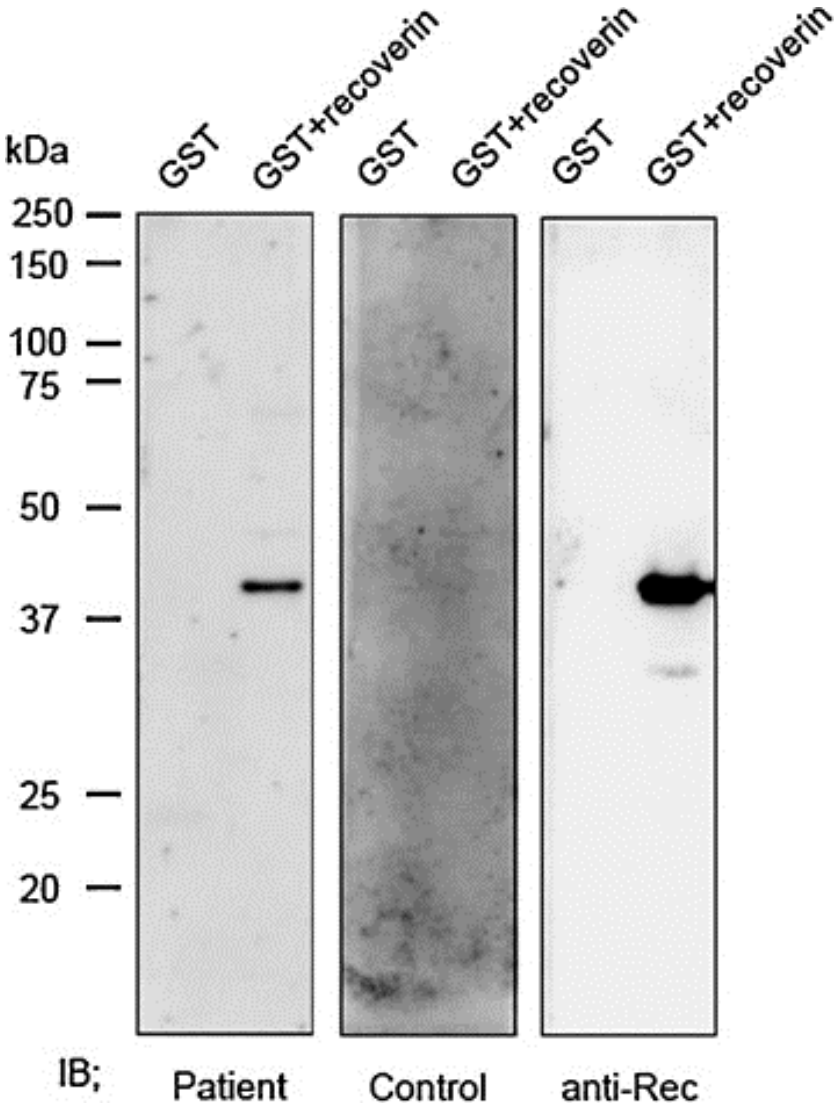
129

Fig. 3.

Western blot analysis revealed the predicted protein band of approximately 49 kDa [recombinant human recoverin (23 kDa)-fusion GST (glutathione S-transferase, 26 kDa) protein] in patient's serum. Patient's and control serum were diluted at 1:2000.

130

Fig. 3


kDa
GST
GST+recoverin
GST
GST+recoverin
GST
GST+recoverin
250
150
100
75
50
37
25
20
IB;
Patient
Control
anti-Rec

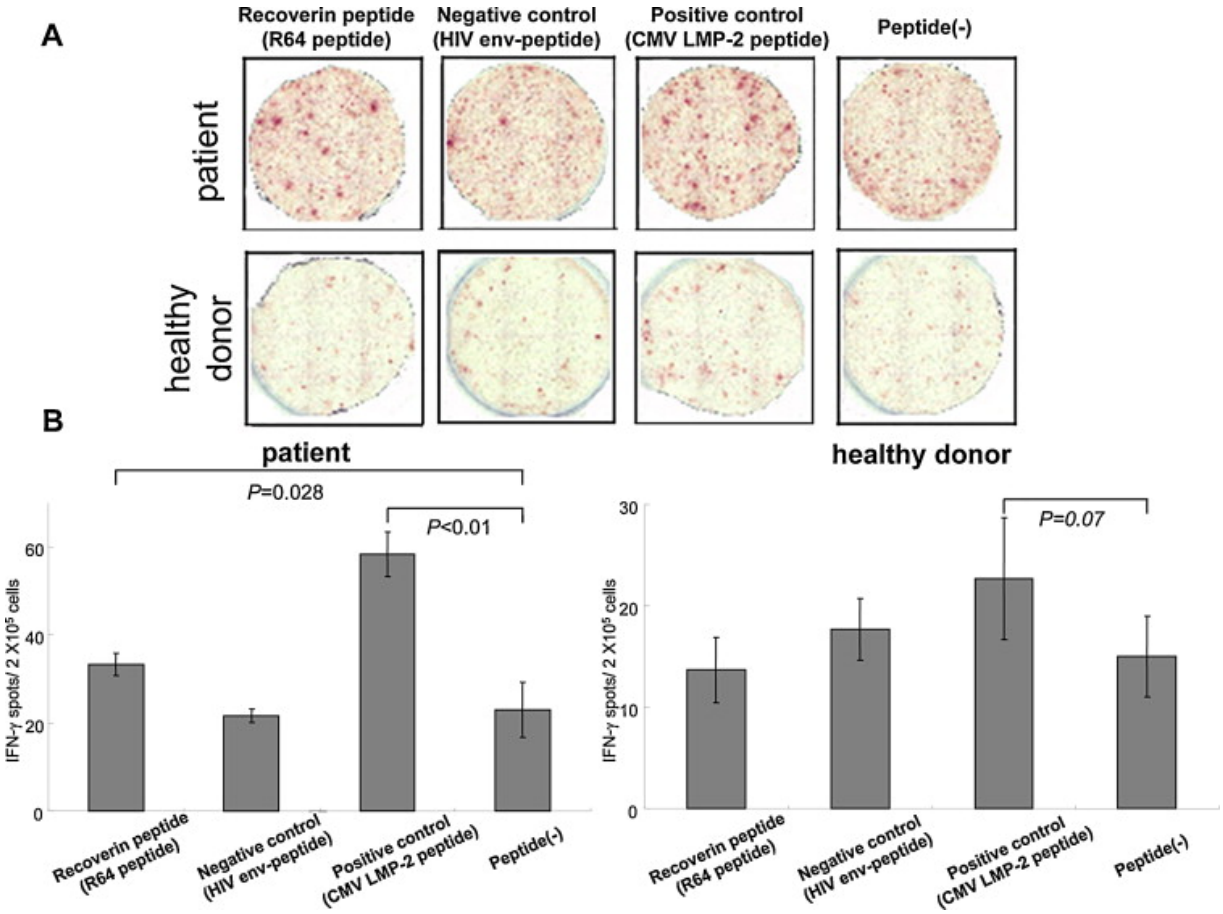
131

Fig. 4.

IFN-γ ELISPOT assay using patient's peripheral blood mononuclear cells stimulated by recoverin peptide in vitro. Recoverin-derived HLA-A24 restricted R64 peptide (AYAQHVFRSF), HIV env-derived peptide (RYLRDQQLLGI) (negative control) and CMV LMP2-derived peptide (TYGPVFMSL) (positive control) were synthesized and purchased from Life Technologies (Carlsbad, CA). (A) The representative data of IFN-γ ELISPOT assay in this patient and a healthy donor. (B) The number of IFN-γ spots that reacted to R64 peptides was significantly higher than that of T cells without peptide in the patient.

132

Fig. 4


A
Recoverin peptide (R64 peptide)
Negative control (HIV env-peptide)
Positive control (CMV LMP-2 peptide)
Peptide(-)
patient
healthy donor
B
patient
healthy donor
P=0.028
P<0.01
P=0.07
IFN-γ spots/ 2 X10⁵ cells
0
20
40
60
10
30
Recoverin peptide (R64 peptide)
Negative control (HIV env-peptide)
Positive control (CMV LMP-2 peptide)
Peptide(-)