



Title	Spontaneous regression of small cell lung cancer combined with cancer associated retinopathy
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1 Spontaneous regression of small cell lung cancer combined with cancer
2 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 retinopathy,

25 Spontaneous regression, Recoverin

26 **Abstract**

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

40 1 . INTRODUCTION

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

54 Spontaneous regression (SR) is defined as the complete or partial
55 disappearance of disease without effective anticancer treatments, continuing
56 for 1 month. Although SR occurs in many types of cancers, it is rare,
57 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 fundoscopic examination showed the

76 appearance of both eyes to be normal, Goldmann perimetry showed a large
77 central scotoma in the right eye and a ring scotoma in the left eye. ERG
78 showed poor responses in both eyes. Recoverin antigen was present in the
79 lung cancer cells and anti-recoverin antibody was observed with high titer
80 (1:2000) in the patient's serum (Fig. 2B, 3). Finally, she was diagnosed with
81 limited disease of SCLC (cT1bN3M0 stage III B) associated with CAR. After
82 diagnosis of SCLC, chest X-ray and CT scan prior to anticancer treatment
83 revealed the SCLC to have partially regressed. Furthermore, levels of both
84 pro-GRP and NSE had already decreased before EBUS-TBNA examination,
85 and decreased further to normal range. *In vitro*, IFN- γ ELISPOT assay was
86 performed, using recoverin peptide to stimulate peripheral blood
87 mononuclear cells taken from the patient. The number of CD8⁺ T cells
88 secreting IFN- γ that reacted to R64 peptide (recoverin-derived HLA-A24
89 restricted peptide R64) was significantly larger than that of T cells without
90 peptide in the patient (Fig. 4 A, B).

91 The patient was treated with chemotherapy comprising cisplatin (80
92 mg/m²) on day 1 and etoposide (100 mg/m²) on days 1, 2, and 3. In addition,
93 oral prednisolone (40 mg daily) was initiated for CAR and gradually tapered

94 over 6 months.

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

100

101 3. DISCUSSION

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

108 Although the reasons for SR remain unclear, a possible hypothesis would
109 be induction of tumor immunologic reaction. Maeda *et al.* have reported
110 that the recoverin-specific cytotoxic T lymphocyte (CTL) was induced in the
111 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.

121

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.

Fig. 1

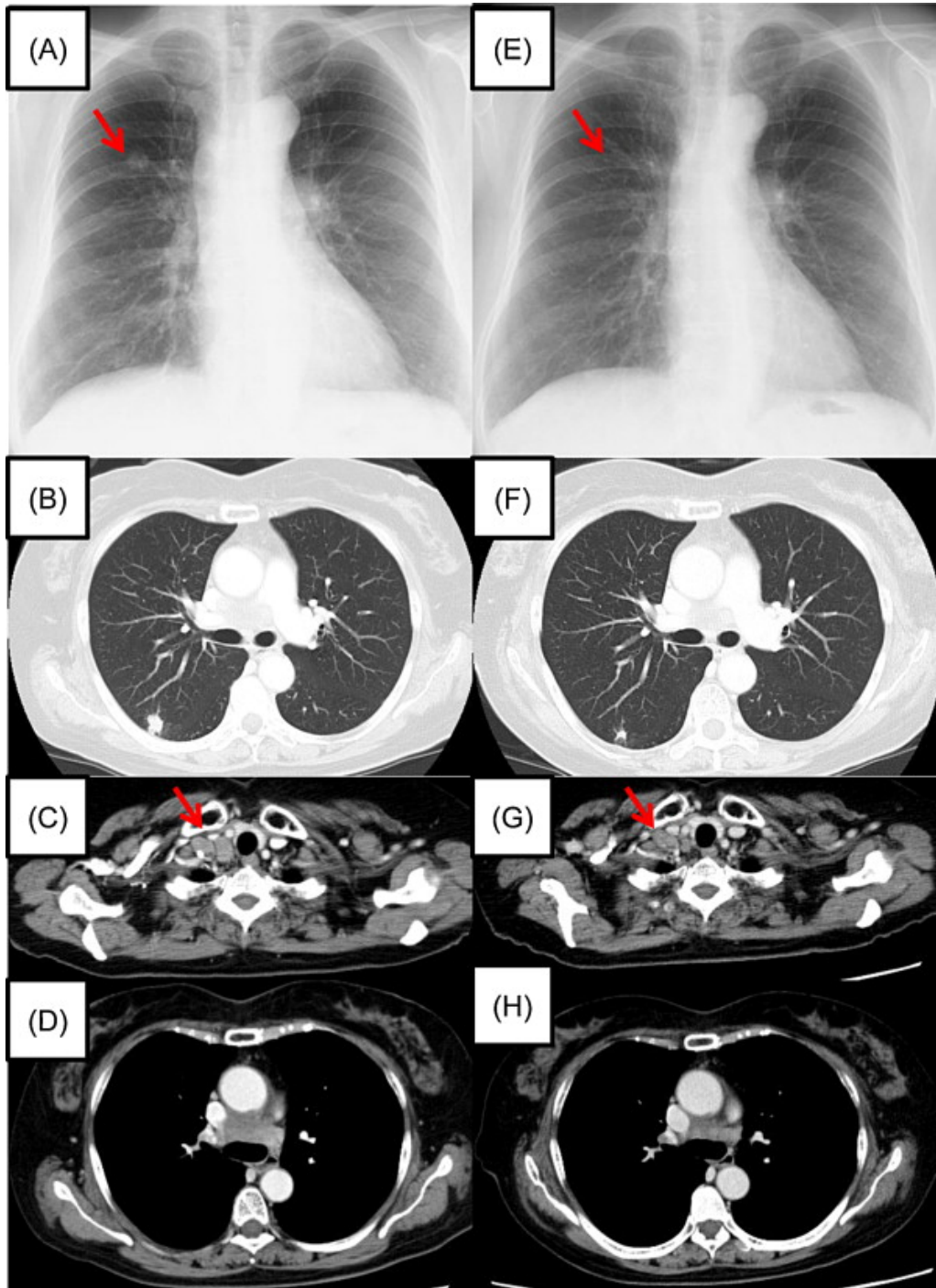
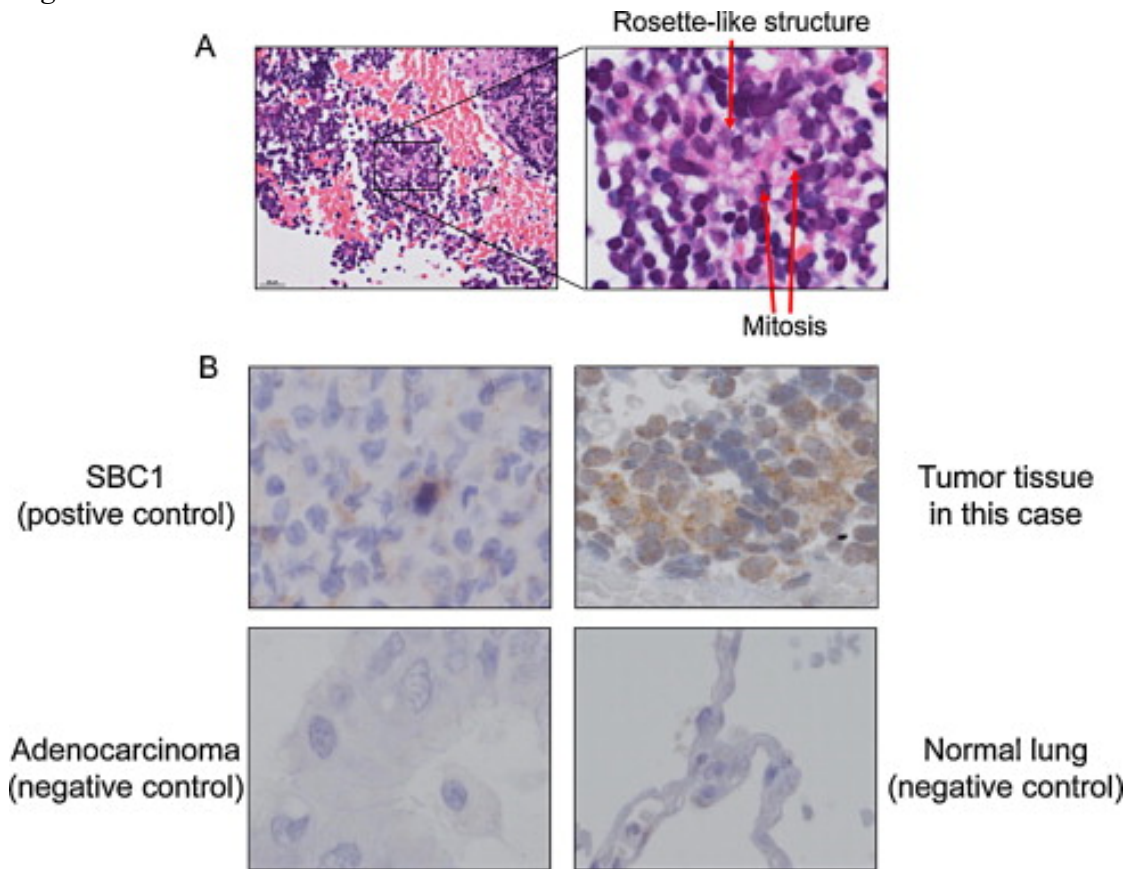


Fig. 2.

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.

127

128 Fig. 2



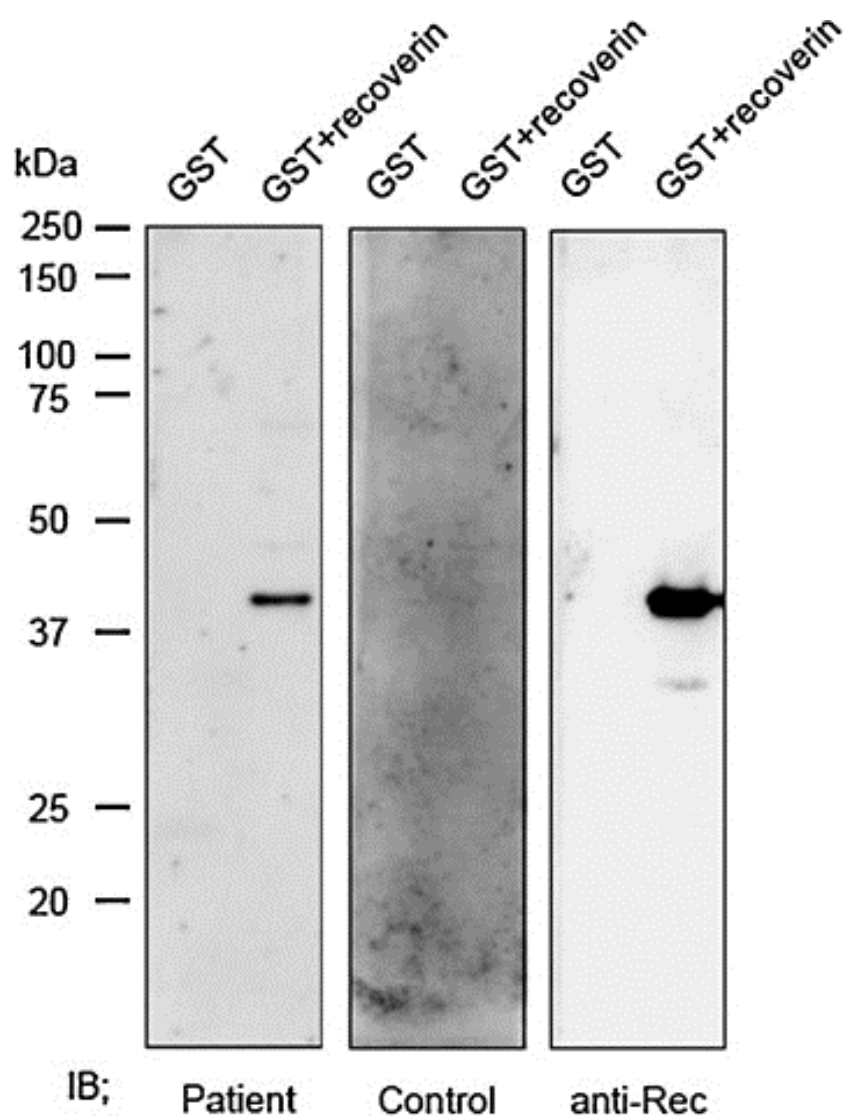
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Fig. 3.

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



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 (AYAQHVF~~R~~SF), HIV env-derived peptide (RYLRDQQLGI) (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.

Fig. 4

