Introduction

Paraneoplastic syndromes are disorders caused by remote effects on various organs without direct invasion or metastasis. Cancer-associated retinopathy (CAR), first reported by Sawyer et al. (1), is a paraneoplastic syndrome associated with epithelial neoplasm, mostly small-cell lung cancer (SCLC). The precise frequency of CAR syndrome in SCLC patients is not clear. CAR is characterized by sudden, progressive deterioration of vision acuity associated with photosensitivity, ring scotoma, attenuated retinal arteriole, visual field defects and an abnormal electroretinogram (2). Retinopathy may develop either before or after the diagnosis of cancer. It is believed that CAR is autoimmune-mediated by autoantibodies directed against retinal photoreceptor proteins, such as recoverin, heat-shock cognate protein 70 and α-enolase (3–5). Autoantibody production may be triggered by immune responses to antigens aberrantly expressed in tumor cells (5).

Regarding CAR treatment, several reports, other than chemotherapy for primary disease, have suggested the effectiveness of corticosteroids alone (2,6–11), combination of corticosteroid and immunoglobulin (12) and plasmapheresis (13); however, standard treatment has not been established. Cases of CAR combined with SCLC have been reported to the present, but there were a small number of reports about treatment of those cases. To date, only 13 cases of corticosteroid therapy alone for CAR with SCLC have been reported in the literature. Both the time of diagnosis and the therapeutic management of this disease are discussed.

Case 1

The patient was a 65-year-old woman with an existing smoking history of 22.5 pack-years. She noticed a bilateral ear-side visual field defect and visited a hospital. She was diagnosed with glaucoma and was treated 4 years before our examination. Her visual acuity was 20/20 OD and 20/25 OS, and her visual field in both eyes was constricted in the Goldmann visual field test. Her visual acuity and visual field were slightly improved after steroid and anticancer therapy. Steroid therapy was effective, although the period from visual symptom onset to therapy was comparatively longer. When cancer-associated retinopathy is suspected, a comparatively large quantity of steroids and anticancer treatment should be combined immediately.
posterior pole region, an optic disc in depth. Chest computed tomography (CT) revealed a solitary nodule in her right lower lobe and mediastinum lymph node enlargement. Magnetic resonance imaging (MRI) of the brain did not show any evidence of tumor infiltration along the optic nerves. Histology obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) demonstrated SCLC. She had limited disease of SCLC with cT1aN2M0. Western blotting using purified human recombinant antigen (recoverin; Ashena Diagnostics, Inc., Worcester, MA, USA; note that this result is available as Supplementary data at http://www.jjco.oxfordjournals.org) revealed CAR autoantibody. Examinations of other autoantibodies against retinal antigens such as heat-shock cognate protein 70, α-enolase and others had not been performed.

Nine months after initial symptom had occurred, she was diagnosed with CAR associated with SCLC. She had received a corticosteroid (prednisolone, 30 mg daily) before her diagnosis, and after 3 months, her visual field defect had slightly improved (Fig. 1C and D) and visual acuity was also improved to 20/63 OD and 20/63 OS. She then received 45 Gy hyperfractionated radiation therapy concurrently with four cycles of cisplatin + etoposide for her good performance status (PS1), and a complete response was achieved.

Her visual acuity deterioration and field defect remained stable, and her visual acuity was 20/50 OD and 20/63 OS when the treatment was completed.

**CASE 2**

The patient was an 88-year-old man with an existing smoking history of 30 pack-years. He had noticed a constriction of the bilateral visual fields and photosensitivity for 4 months. His visual symptoms gradually progressed and he visited the Department of Ophthalmology of our hospital. In the first examination, his visual acuity was 30/20 OD and 20/16 OS and a Goldmann visual field test of the right eye showed an ear-side defect and ringed scotoma (Fig. 2A and B). Fundus examination of both eyes showed attenuated retinal arteriole. Electoretinogram showed slightly decreased a and b waves. His visual acuity

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Figure 1. Humphrey visual field perimeter results of Case 1 showing a nasal-side defect in the right eye (mean, −23.86 dB) (A) and little response in the left eye (mean, −29.64 dB) (B). (C) Three months later, after corticosteroid administration, there was no change in the visual field defect in the right eye (mean, −26.02 dB). (D) Three months later, there was a slight improvement in the right eye (mean, −28.53 dB).
deteriorated to 1.0 OD and 0.9 OS and a ring scotoma was detected. Brain MRI did not show any evidence of tumor. Chest CT showed two mass lesions in her left anterior chest wall and posterior mediastinum. EBUS-TBNA was performed and the diagnosis of SCLC was made. Anterior chest wall lesion was considered as an extrapulmonary metastasis and his disease stage was cT3N0M1b (extensive disease). Western blot analysis of anti-recoverin antibody was negative (this result is available as Supplementary data at http://www.jjco.oxfordjournals.org). Examinations of other autoantibodies had not been conducted. We diagnosed CAR based on the clinical manifestation, such as progressive loss of vision, photosensitivity, ring scotoma and a visual field defect, and the presence of cancer. He was given oral prednisolone (25 mg daily) immediately after the diagnosis of CAR because of the rapid progression of visual acuity deterioration. On the basis of good PS (PS1) despite an old age, chemotherapy with cisplatin and etoposide was administrated 1 month after the diagnosis of CAR. Although initial reports failed to show visual improvement with prednisone therapy alone (1,15), most other researchers have demonstrated that steroid therapy improved visual function or at least prevented it from worsening (2,6–11,16–18). It is considered that corticosteroid therapy is effective for control of CAR. In this report, we summarize the clinical features of 15 patients diagnosed with CAR with SCLC and

**DISCUSSION**

Anti-recoverin antibody in Case 2 was not detected. Recoverin is the most common retinal antigen related to CAR. The measurement of anti-recoverin antibody provides crucial evidence supporting the diagnosis of CAR; however, we cannot exclude CAR even when anti-recoverin antibody is not detected because generally the positive rate of the anti-recoverin antibody is not so high (14). Since the patient in Case 2 has clinical findings of CAR, he was diagnosed with CAR, despite negative for anti-recoverin antibody examination.

As for the treatment of our cases, both the visual field and visual acuity improved with steroid therapy alone before anticancer therapy in Case 1 and the visual field improved although tumor shrinkage was not achieved in Case 2. Although initial reports failed to show visual improvement with prednisone therapy alone (1,15), most other researchers have demonstrated that steroid therapy improved visual function or at least prevented it from worsening (2,6–11,16–18). It is considered that corticosteroid therapy is effective for control of CAR. In this report, we summarize the clinical features of 15 patients diagnosed with CAR with SCLC and
In 13 of 15 SCLC patients with CAR (87.7%) who received corticosteroid therapy, visual function transiently recovered (2,6–11,16,18). In those 13 patients, the mean dose of corticosteroid administered at initial treatment was 57.1 mg (25–100) and the mean duration from CAR symptom onset to treatment was 2.75 months. In addition, in most cases, the onset of retinopathy preceded the diagnosis of SCLC (1,2,7–11,13,18–20). In one patient whose visual deterioration progressed after initial steroid therapy, a comparatively lower dose of steroid for CAR may have been involved (15). The literature might suggest that a sufficient dose of steroid was necessary to restore visual function or prevent its progression. In addition, it is assumed that the duration from visual symptom onset to the start of steroid therapy is important because treatment delay may lead to irreversible injury of photoreceptor cell progression. In contrast, the visual acuity of the patients reported by Boucher and Allaire markedly improved, despite treatment delay. In our cases, although the steroid dose was lower than in previous reports and the period before starting therapy for CAR was comparatively long, their visual acuity and visual field slightly improved. Our cases and Boucher’s case differ from Sawyer’s and Suzuki’s cases in the use of anticancer therapy. This suggests that the combination of anticancer therapy and systemic steroid therapy may have affected the improvement of CAR syndrome. In addition, if the patients had been treated earlier with a sufficient steroid dose, their visual function might have improved much more.

In this report, the visual symptom of two patients preceded the diagnosis of SCLC and they were diagnosed with CAR in light of progressive visual impairment and tumor presence with/without the detection of anti-recoverin antibody. We were able to stabilize the visual acuity and visual field by immediately administering a steroid and anticancer therapy. When CAR is suspected, a comparatively large quantity of steroids and anticancer treatment should be combined immediately.

Conflict of interest statement
None declared.

References
4. Ohguro H, Ogawa K, Maeda T, Maeda A, Maruyama I. Cancer-associated retinopathy induced by both anti-recoverin and

Table 1. Summary of clinical data of CAR patients with SCLC who received corticosteroid therapy alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Autoantibody</th>
<th>Sex/age</th>
<th>Stage</th>
<th>Anticancer therapy for CAR</th>
<th>Initial dose (mg)</th>
<th>From CAR onset to diagnosis of SCLC (months)</th>
<th>From CAR onset to steroid therapy (months)</th>
<th>Effect of treatment for CAR</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Sawyer et al.</td>
<td>NA</td>
<td>M/65</td>
<td>LD</td>
<td>None</td>
<td>100</td>
<td>4</td>
<td>6</td>
<td>Progression</td>
<td>(1)</td>
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<td>Kashiwabara et al.</td>
<td>23 kDa</td>
<td>F/70</td>
<td>LD</td>
<td>CBDCA + VP-16</td>
<td>40</td>
<td>−12</td>
<td>0.5</td>
<td>Imp</td>
<td>(6)</td>
</tr>
<tr>
<td>Matsuura et al.</td>
<td>23 kDa</td>
<td>M/69</td>
<td>ED</td>
<td>CBDCA + VP-16</td>
<td>20</td>
<td>1.5</td>
<td>2</td>
<td>Imp</td>
<td>(9)</td>
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<tr>
<td>Ohnishi et al.</td>
<td>24 kDa, 48 kDa</td>
<td>M/50</td>
<td>LD</td>
<td>CT</td>
<td>NA</td>
<td>3</td>
<td>0.5</td>
<td>Imp</td>
<td>(10)</td>
</tr>
<tr>
<td>Keltner et al.</td>
<td>23 kDa</td>
<td>M/68</td>
<td>ED</td>
<td>CDDP + VP-16</td>
<td>100</td>
<td>5</td>
<td>3</td>
<td>Imp</td>
<td>(7)</td>
</tr>
<tr>
<td>Takahashi et al.</td>
<td>20 kDa, 37 kDa</td>
<td>M/70</td>
<td>LD</td>
<td>CDDP + VP-16 + RT</td>
<td>60</td>
<td>2</td>
<td>1</td>
<td>Imp</td>
<td>(18)</td>
</tr>
<tr>
<td>Boucher and Allaire</td>
<td>NA</td>
<td>M/58</td>
<td>NA</td>
<td>CT</td>
<td>80</td>
<td>5</td>
<td>6</td>
<td>Imp</td>
<td>(16)</td>
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<tr>
<td>Suzuki et al.</td>
<td>62 kDa</td>
<td>F/63</td>
<td>NA</td>
<td>None</td>
<td>25</td>
<td>−21</td>
<td>5</td>
<td>Progression</td>
<td>(15)</td>
</tr>
<tr>
<td>Jacobson et al.</td>
<td>23 kDa, 48 kDa</td>
<td>M/67</td>
<td>LD</td>
<td>CDDP + VP-16</td>
<td>80</td>
<td>1</td>
<td>0.5</td>
<td>Imp</td>
<td>(2)</td>
</tr>
<tr>
<td></td>
<td>23 kDa</td>
<td>M/71</td>
<td>LD</td>
<td>CPA + ADR + VCR</td>
<td>60</td>
<td>5</td>
<td>4</td>
<td>Imp</td>
<td></td>
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<tr>
<td>Rizzo and Gittinger</td>
<td>48 kDa</td>
<td>M/59</td>
<td>NA</td>
<td>CDDP + CPA + ADR + VP-16 + RT</td>
<td>80</td>
<td>NA</td>
<td>0.5</td>
<td>Imp</td>
<td>(11)</td>
</tr>
<tr>
<td></td>
<td>23 kDa</td>
<td>M/67</td>
<td>NA</td>
<td>CPA + ADR + VP-16</td>
<td>80</td>
<td>2</td>
<td>2</td>
<td>Imp</td>
<td></td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>23 kDa</td>
<td>M/66</td>
<td>LD</td>
<td>CDDP + VP-16 + RT</td>
<td>30</td>
<td>5</td>
<td>NA</td>
<td>Imp</td>
<td>(8)</td>
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<td>Sakamori et al.</td>
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<td>F/65</td>
<td>LD</td>
<td>CDDP + VP-16</td>
<td>30</td>
<td>10</td>
<td>9</td>
<td>Imp</td>
<td>Present case</td>
</tr>
<tr>
<td>Negative (23 kDa)</td>
<td>M/85</td>
<td>ED</td>
<td>CBDCA + VP-16</td>
<td>25</td>
<td>4</td>
<td>4</td>
<td>Imp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAR, cancer-associated retinopathy; SCLC, small-cell lung cancer; NA, data not available; LD, limited disease; CBDCA, carboplatin; VP-16, etoposide; Imp, improvement; ED, extensive disease; CT, chemotherapy; CDDP, cisplatin; RT, radiotherapy; CPA, cyclophosphamide; ADR, adriamycin; VCR, vincristine.

1Induction of high-dose methylprednisolone.