CASE REPORT

A Small Cell Lung Cancer With Cancer-associated Retinopathy: Detection of the Primary Site in the Lung 15 Months After Resection of Metastatic Mediastinal Lymphadenopathy

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ABSTRACT —— ***Background.*** Cancer-associated retinopathy and metastatic thoracic lymphadenopathy of unknown origin are rare phenomena in lung cancer. A patient with cancer-associated retinopathy (CAR) from small cell lung cancer (SCLC) is described. ***Case.*** A 67-year-old woman presented with mediastinal lymphadenopathy and had visual disturbance of sudden onset. The mediastinal nodes, removed under thoracotomy, pathologically showed oat cell type small cell carcinoma. No primary tumor was found despite a thorough workup. Although anti-CAR antigen antibody was not detected, CAR was diagnosed according to multiple clinical examinations. A primary SCLC was detected in the right lower lobe 15 months after resection of the mediastinal nodes. ***Conclusion.*** This case demonstrates that undetectably small tumors can produce a large mass by lymph node metastasis and cause CAR. (*JJLC.* 2004;44:43-48)

KEY WORDS —— Cancer-associated retinopathy (CAR), Small cell lung cancer (SCLC), Paraneoplastic syndrome (PNS), Retinal autoantibodies

INTRODUCTION

Paraneoplastic syndromes (PNS) are disorders caused by remote effects of tumors in various organs without direct invasion or metastasis. Cancer-associated retinopathy (CAR) is a PNS causing retinal dysfunction leading to ocular symptoms. CAR is believed to be caused by autoantibodies against various retinal antigens (recoverin, neurofilaments, or other proteins). Among these, only anti-recoverin antibodies can be detected by a commercially available test, so a diagnosis of CAR cannot be ruled out even if the anti-recoverin antibody is not detected.

On the other hand, occurrence of carcinoma in mediastinal or hilar lymph nodes with no known primary site is uncommon. In some of these cases, uncertainty persists as to whether the lymph node cancer is primary or metastatic. We report a case of small cell carcinoma in mediastinal lymph nodes with no known primary site that caused CAR. To the best of our knowledge, this is the first report of a patient with both CAR and metastatic thoracic lymph nodes with no known primary site, although a primary lung cancer was detected many months later.

CASE REPORT

A 67-year-old woman with fever and cough consulted a local physician on May 10, 2001. Her past medical history included cerebral infarction, diabetes mellitus, and angina pectoris, as well as incidentally diagnosed glaucoma that was treated uneventfully with collyrium beginning in January 2001. She had had a left temporal artery-middle cerebral artery bypass operation 10 years previously. She had smoked half a pack of cigarettes daily for more than 35 years. A chest roentgenogram suggested pneumonia in the right middle lobe. Computed tomography (CT) disclosed lymphadenopathy in the upper mediastinum and advanced emphysema of bilateral lungs.

The pneumonia was treated with antibiotics, and the abnormal shadow in the right middle lobe disappeared. The patient's visual acuity suddenly deteriorated in August 2001. An ophthalmologist suspected metastatic uveitis, but no diagnosis was made.

The patient was referred to our hospital for diagnostic

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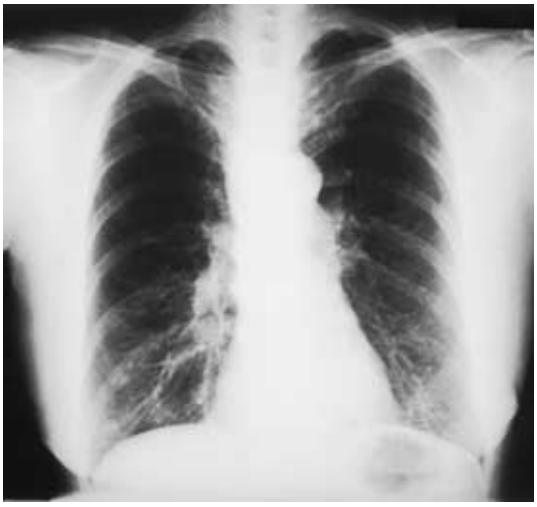

Figure 1. A chest roentgenogram reveals slight prominence of the right upper mediastinum.

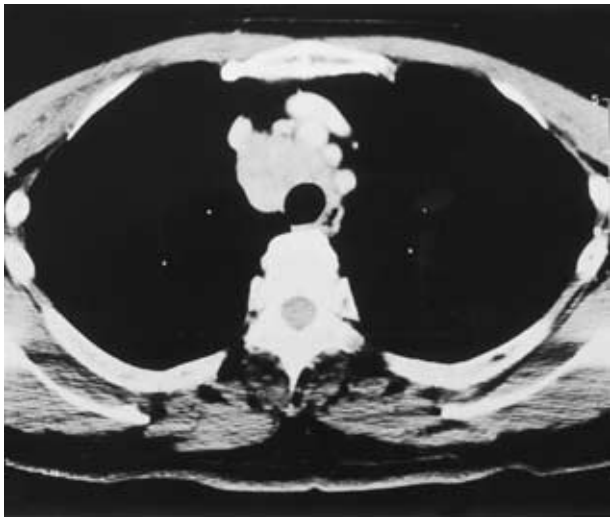

Figure 2. Computed tomography of the chest shows a mass compressing the right brachiocephalic vein.

evaluation of mediastinal lymphadenopathy and elevated serum concentrations of carcinoembryonic antigen (CEA), and was admitted on August 21, 2001. Fiberoptic upper gastrointestinal endoscopy and colonoscopy did not detect any cancer, neither did a gynecologic survey. She was referred to the Department of Thoracic Surgery to obtain mediastinal tissue for pathologic diagnosis.

The patient's height was 156.5 cm, and her weight was 51.5 kg. The blood pressure was 138/70 mmHg, with a pulse rate of 88 beats/min. Heart and breath sounds were normal. No superficial lymphadenopathy was evident. The peripheral blood count was normal. Serologic tests for hepatitis C antibody were positive. Blood chemistry results were within normal limits except for increased triglyceride. The CEA concentration was 8.3 ng/ml. Pulmonary function values were normal in spite of severe emphysema demonstrated by chest CT. Results of arterial blood gas analysis were $PaCO_2$, 43.9 mmHg; PaO_2, 71.1 mmHg; and pH, 7.385. A chest roentgenogram revealed slight prominence of the right upper mediastinum (Figure 1). Chest CT showed a mass in the upper mediastinum extending anterolaterally to compress the right brachiocephalic vein (Figure 2). The pneumonic shadow in the right middle lobe that had been seen in the previous CT had disappeared, but no parenchymal mass could be detected. Severe emphysema was demonstrated bilaterally in the upper lobes and the basal areas of the lower lobes. MRI of the brain revealed no metastatic lesion. No abnormality in the tracheal wall or in any visible bronchus could be seen at bronchoscopy.

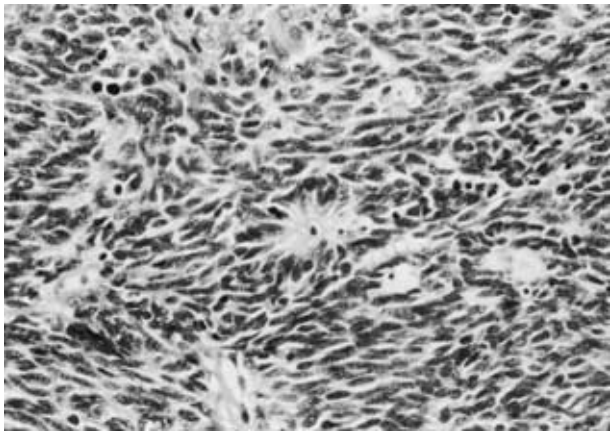

Figure 3. The histologic pattern of the tumor in thoracic lymph nodes indicates oat cell type small cell carcinoma (hematoxylin and eosin, ×100).

Operative findings. As a systemic lymphatic disease such as lymphoma was suspected, thoracoscopic needle biopsy was done on August 29, 2001. However, pathologic diagnosis of a frozen section of the specimen was uncertain. The entire mass then was resected via a thoracotomy. The tumor was dissected easily from surrounding tissues. As a small mass was palpated in the right middle lobe, partial resection of the lung was performed.

Pathologic findings. The mediastinal tumor measured 58×33×30 mm. Macroscopically, the cut surface of the

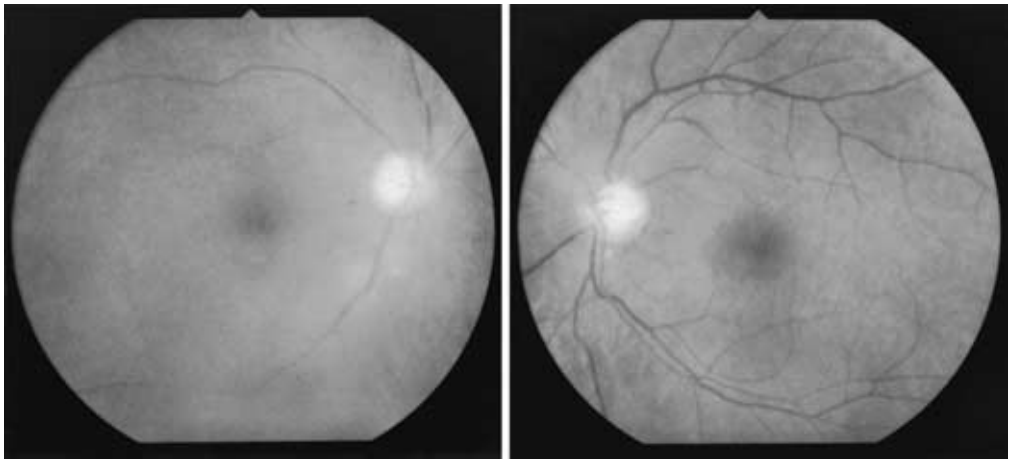

Figure 4. Fundus photograph showing marked narrowing of retinal arteries and their branches in the right eye (**A**) compared with the left eye (**B**).

tumor showed a multilobular structure. The histopathologic diagnosis was oat cell type small cell carcinoma (Figure 3). The microscopic diagnosis of the resected pulmonary tissue was bronchiolitis, with no tumor seen.

Ophthalmologic examinations. The central portion of the right visual field showed a severe visual defect, and light was perceived minimally in the periphery. On fundoscopic examination of the right eye, reduction in the caliber of the retinal arterioles was evident (Figure 4A). An electroretinogram (ERG) detected no response (Figure 5). Vitreous cells were observed ophthalmoscopically. Although anti-CAR antigen antibody was negative (Athena Diagnostics, Worcester, MA), a diagnosis of cancer-associated retinopathy (CAR) was made on the basis of clinical ophthalmologic findings.

Postoperative course. The patient received one cycle of chemotherapy (cisplatin and etoposide) after surgery. She declined a second cycle because of gastrointestinal side effects. As her vision gradually deteriorated, she underwent corticosteroid therapy in September 2002, but without therapeutic effects. In October 2002, MRI of the brain revealed a cerebral metastatic lesion without clinical symptoms. A stereotactic gamma-knife radiosurgery was directed against this metastatic tumor.

Detection of the primary tumor. In December 2002,15 months after the first operation, a follow-up chest radiograph revealed a coin lesion in the right lower lobe. Chest CT confirmed the presence of a mass in the right lower lobe (Figure 6B). In a careful review of the previous CT, a minute shadow that represented the origin of the primary tumor was identified (Figure 6A). The tumor was resected thoracoscopically on January 27, 2003. The pathologic diagnosis was oat cell type small cell lung cancer, identical to the resected mediastinal tumor. The patient is nearly blind in the right eye and only perceives hand motion on acuity testing in the left eye at the time of submission of this paper (September 2003).

DISCUSSION

Paraneoplastic syndromes (PNS) are clinical phenomena caused by remote effects of malignant neoplasms as opposed to direct invasion or metastasis. Among these, visual disturbance reflecting retinal degeneration has been termed paraneoplastic retinopathy (PNR), visual paraneoplastic syndrome (VPNS), or cancer-associated retinopathy (CAR). In 1976 Sawyer et al.[1] first reported blindness caused by retinal degeneration of obscure pathogenesis in three patients with cancer. Kornguth et al.[2] found anti-retinal ganglion cell antibody in the serum of patients with CAR and suggested immune reactions as the etiology of CAR. Keltner et al.[3] reported that steroid therapy could benefit patients with CAR, and advocated an autoimmune pathogenesis. Thirkill et al.[4] found an antiretinal antibody, reactive against a 23-kDa protein that they called *the CAR antigen*, in sera of patients with CAR. Polans et al.[5] reported a 26-kDa protein, later identified as recoverin, which is believed to represent the CAR antigen. Presently, many antibodies with various molecular weights are believed to be involved in various cases. Intracellular recoverin has been demonstrated in an

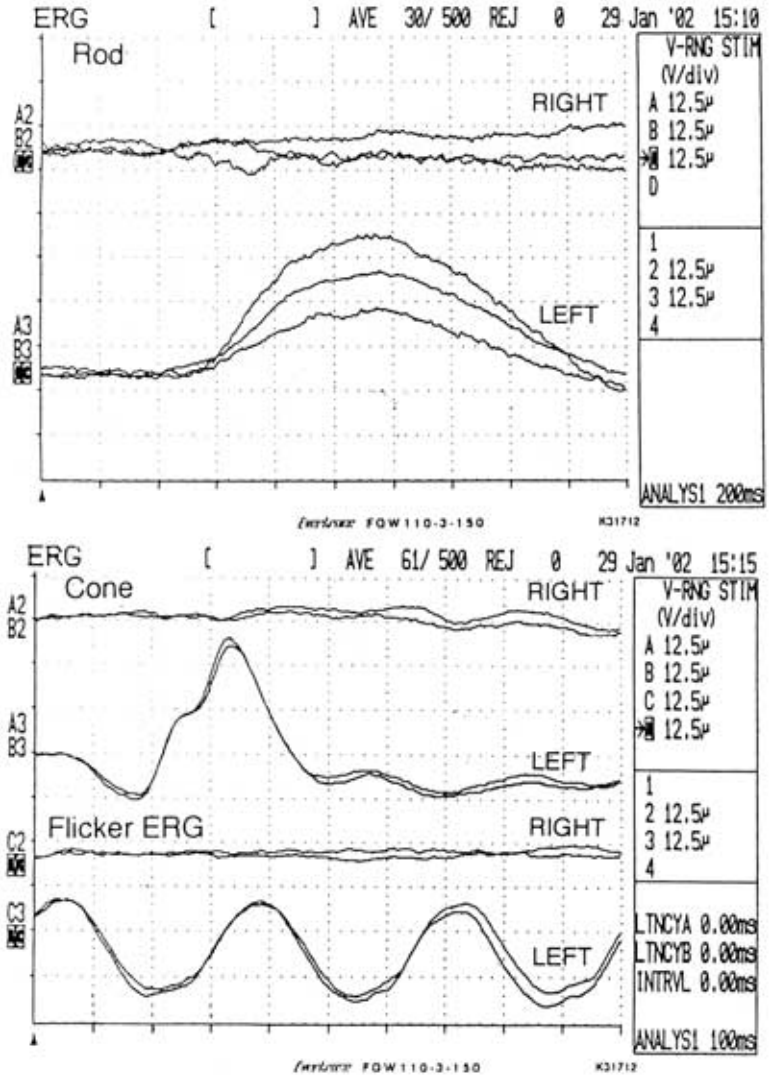

Figure 5. Electroretinography: No retinal response was detected in the right eye.

SCLC line from a patient with CAR, [6] and anti-recoverin antibody has been detected in low titers even in sera from some SCLC patients without CAR.[7] These findings represent the basis for a persuasive hypothesis concerning the pathogenesis of CAR. SCLC cells, which have a neuroendocrine origin, ectopically produce recoverin or other proteins. Autoantibodies against these antigens cross-react with native recoverin (or other proteins) in retinal tissues, resulting in degeneration of the retina and visual disturbance. However, not every CAR occurs in SCLC patients.We collected 57 cases of CAR that had been reported until recently including our case (Table 1). The percentage of SCLC in all CAR was 75.4%. It is difficult to explain why other cancers besides small cell cancer cause CAR.

Controversy persists concerning metastatic mediastinal and/or hilar lymphadenopathy of unknown origin.[8-15] Some authors maintain that these cancers in thoracic lymph nodes are primary, not metastatic. Riquet [15] microscopically demonstrated that nonneoplastic glandular tissue can exist in lymph nodes, representing a potential origin for carcinoma. Most cases of carcinoma found solely in nodes have been reported from Japan, [8-10,12,14] which might reflect relatively aggressive treatment for presumed lung cancer with evidence of metastasis to mediastinal lymph nodes.Because resection is performed

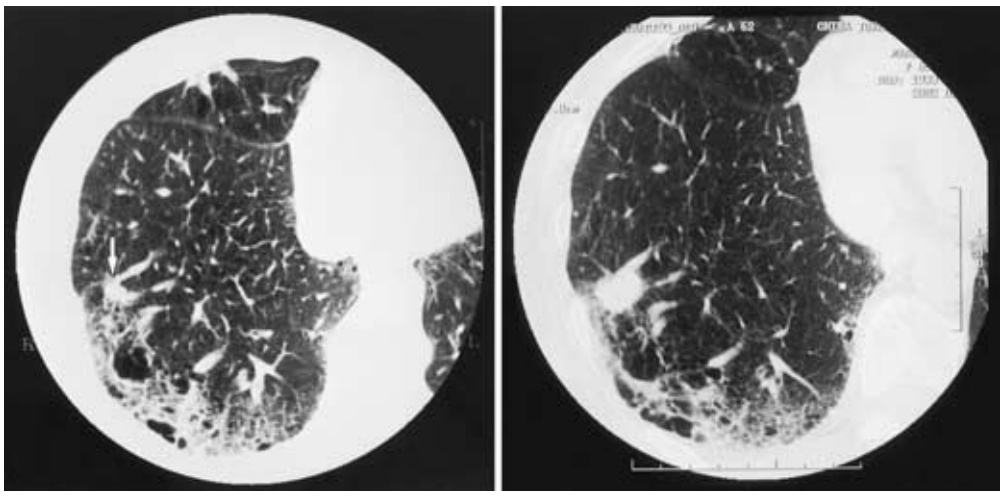

Figure 6. **A.** A minute area with altered opacity (arrow) can be recognized retrospectively in the right lower lobe by computed tomography (CT) obtained just before the first operation. **B.** A primary tumor at the same site is evident by CT performed 15 months later.

Table 1. Primary organ and type of tumor in reported cases of CAR

Primary organ	No. of cases	Pathological diagnosis
Lung	43	SCLC(37), adeno ca(4), unclear(1), undifferentiated ca(1)
Uterus	6	small-cell ca(2), endometrial ca(2), sarcoma(1), undifferentiated ca(1)
Stomach	2	carcinoma(2)
Thymus	2	invasive thymoma(2)
Breast	1	adeno ca(1)
Unknown	3	< biopsy site > vagina(1), intrapelvic mass(1), supraclavicular lymph node(1)
Total	57	

less frequently for lung cancer with overt thoracic lymph node involvement in Western countries, these lymph nodes are less often studied. Our search disclosed 105 such cases of cryptogenic intranodal carcinoma in the Japanese and international literatures. Among these, primary tumors were identified subsequently in only 8 cases (8.2%; 7 from lung, 1 from kidney). The longest interval to detection was 65 months after the first operation.[14] In our case, primary lung cancer appeared 15 months after resection of the metastatic mediastinal lymph nodes, and a primary mediastinal origin had been suspected. Thus uncertainty should be allowed to persist about the origin of nodal carcinoma with no known primary tumor.

Of 97 patients with resected thoracic lymph node cancer of unknown primary site, 10 (10.3%) attained cancer-free survival more than three years postoperatively. And six of them (6.2%) had survived more than five years without recurrence with one exceptional case, in which a primary site appeared 65 months postoperatively.[14] We therefore believe that resection of these lesions is indicated.

CONCLUSION

In a patient with SCLC associated with CAR, metastatic tumor in mediastinal lymph nodes had been resected 15 months before any primary cancer appeared in the lung. CAR also antedated detection of the lung tumor. Although antibodies to *the CAR antigen* (one of several CAR-related antigens) could not be detected, the clinical courses of sudden and ongoing visual deterioration as well as ophthalmologic findings were diagnostic. We anticipate that future availability of tests for antibodies against other CAR-related antigens will facilitate early diagnosis.

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