Lung cancer-associated cognitive impairment in a patient with Alzheimer's disease pathology: A case report

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Abstract

Pathologic amyloid β and tau protein accumulation in the cerebral cortex does not necessarily lead to a diagnosis of Alzheimer's disease. Our current report presents a patient with Alzheimer's disease pathology who presented general cognitive impairment we considered derived from the lung cancer itself, without metastasis.

KEYWORDS

lung cancer, cognitive impairment, Alzheimer's disease, mild cognitive impairment, amyloid β, tau protein

1 | INTRODUCTION AND BACKGROUND

Alzheimer's disease (AD) is the most common neurodegenerative disease accompanied by dementia, which is considered due to the deposition of pathologic amyloid β and successive pathologic tau protein. The main clinical features of AD are an amnestic presentation, which includes learning impairment and problems recalling recently learned information, as well as nonamnestic impairments.[1] Regional atrophy and hypoperfusion

are typically observed in the medial temporal lobes, as shown by magnetic resonance (MR) imaging and [^{123}I] iodoamphetamine single-photon emission computed tomography (IMP-SPECT), respectively. Mild cognitive impairment (MCI) is defined as the prodromal stage of dementia, with amnestic MCI considered that due to AD and supported by pathophysiological evidence.[2]

Sleep apnea syndrome (SAS) can cause cognitive impairment, which can be improved through continuous positive airway pressure (CPAP) treatment.[3] Additionally, cancer in non-central nervous system malignancies can cause cancer-related cognitive impairment.[4]

We present a case of a right-handed 64-year-old Japanese man who visited our clinic with his wife, complaining of memory impairment. The patient was suspected of early-stage MCI due to AD based on IMP-SPECT findings. Pathologic amyloid β and tau protein deposition in the brain was also shown using ^{11}C-Pittsburgh compound-B (PiB) positron emission tomography (PET) and ^{18}F-THK5351 (THK5351)-PET, respectively.[1] During the observation, the patient was diagnosed with SAS and treated successfully, although his cognitive impairment progressed. Eighteen months after the baseline visit, the patient might be diagnosed with early-stage AD. Nineteen months after the baseline visit, the patient was diagnosed with lung cancer without metastasis and underwent surgery. Several months after the surgery (2 years after the baseline visit), his cognitive ability as evaluated by neurocognitive testing showed significant improvement.

The cognitive impairment in our current case can therefore be considered to have been caused by carcinogenesis derived from the patient's lung cancer. When diagnosing AD, it is important to collectively consider the patient's physical illness rather than based solely on the results of neurocognitive tests and pathophysiological findings.

2 | CASE PRESENTATION

The wife of a 64-year-old right-handed Japanese man complained that her husband's cognitive function had begun to deteriorate; for example, he had difficulty in performing simple calculations and could not recognize his old friends. His medical history showed no illnesses, and he had no previous history of psychiatric disorders. His educational level was graduation from high school. His wife considered that these impairments could be due to problems at his job. The patient had begun to talk about being eager to quit his job and complain about not feeling well. His wife suspected memory impairment in her husband's daily life. When he visited our clinic accompanied by his wife, the patient calmly stated that he was not well accustomed to his new job. Although his mental condition showed nothing particular, his episodic memory appeared to be slightly impaired based on medical interviews by a certified psychiatrist. Neurocognitive tests, MR imaging, and IMP-SPECT were therefore performed (Table 1, Figures 1a, 2a, 2b). The results of the neurocognitive tests showed that the patient's cognitive ability was normal (Table 1) ; however, his structural and functional brain images suggested an AD pattern (Figures 1a, 2a, 2b). It was because bilateral superior parietal lobes showed slight atrophy for his age on MR images, and because hypoperfusion was observed in the bilateral parietal-temporal association areas, posterior cingulate gyrus and precuneus, and frontal association areas, predominantly in the right cerebral hemisphere, based on IMP-SPECT (Figures 1a, 2a, 2b).

Three months after the first visit, the attending psychiatrist suspected that the patient might have SAS, based on the medical interviews. The psychiatrist referred the patient to a medical sleep center, where the patient was diagnosed with moderate to almost severe SAS based on the results of a sleep polysomnography test, which were as follows: apnea-hypopnea index, 29.3; oxygen desaturation index, 17.3; minimum oxygen saturation, 93%; and arousal index, 38.0. CPAP was therefore introduced, which improved his SAS.

The patient underwent neurocognitive tests at one year and at 18 months after the baseline visit (Table 1), which showed, during the 6 months, gradually worsening scores on the mini-mental state examination (MMSE). The patient was diagnosed with non-amnestic MCI or early-stage AD. Eighteen months after the baseline visit, the patient also underwent PiB-PET and THK5351-PET, which revealed positive pathological amyloid β and tau protein accumulation (Figures 3a, 4a), thereby indicating an AD neurological disease.[5,6] At that point, the results of MR imaging were almost identical to those of the baseline visit (Figure 1a, 1B).

Nineteen months after the baseline visit, lung cancer (right, S2, T3N0M0) was detected in the patient, but his only clinical feature was a dry cough, which his wife stated appeared occasionally. No metastasis was found, the tumor was surgically removed, and the pathology indicated adenosquamous carcinoma. Per the surgeon's instructions, the patient ceased the CPAP therapy for 2 months after the surgery.

Two years after the baseline visit, the patient's MMSE score showed that his general cognitive ability had improved after the resection surgery for his lung cancer (Table 1). However, his neurocognitive test scores were slightly lower 3 years after the baseline visit compared with those 2 years after the baseline visit (Table 1). The MR, PiB-PET, and THK5351-PET images are shown in Figures 1c, 3b, and 4b, respectively. The results of MR imaging were almost identical to those performed at baseline visit and at 18 months after the baseline visit (Figure 1a, 1b, 1c). However, the deposition of pathologic tau protein had slightly increased.

3 | TIMELINE

3-1 | Baseline visit

Performance of neuropsychological tests, brain MR imaging, and IMP-SPECT

3-2 | Three months from baseline visit

Diagnosis of SAS and start of CPAP

3-3 | One year from baseline visit

Performance of neuropsychological tests

3-4 | Eighteen months from baseline visit

Performance of neuropsychological tests, MR imaging, PiB-PET, and THK5351-PET

3-5 | Nineteen months from baseline visit

Detection of lung cancer and surgical removal of the tumor. Interruption of CPAP for 2 months after the surgery.

3-6 | Two years from baseline visit

Performance of neuropsychological tests

3-7 | Three years from baseline visit

Performance of neuropsychological tests, MR imaging, PiB-PET, and THK5351-PET

4 | DISCUSSION

To our knowledge, our report is the first to show that lung cancer itself without metastasis can cause cognitive impairment. Cancer of the non-central nervous system has been shown to induce cognitive impairment; however, its mechanism has not been well studied.[7] Moreover, little is known of the cognitive function of patients with cancer prior to surgery, with only 3 studies having evaluated the cognitive function of patients newly diagnosed with breast cancer.[7]

The SAS and pathophysiological evidence in isolation cannot fully explain the patient's cognitive impairment. SAS can induce cognitive impairment, especially the obstructive form of SAS, which has been associated with general cognitive impairment.[8] Our current case presented general cognitive impairment one year after the baseline visit, which gradually worsened despite the successful introduction of CPAP. The patient did not show the typical cognitive impairment of AD, although the pathophysiological findings using PiB-PET, THK5351-PET, and IMP-SPECT indicated AD type impairment.

A limitation of our current report is that, although we observed the patient longitudinally and in detail, we had only one case. Cohort studies investigating non-central nervous system cancers, divided by type, remain to be performed.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

MT conceived of the idea, directed and planned the study, performed the literature search, helped create the table and figures, analyzed the neurocognitive and neuroimaging data, and revised and submitted the manuscript; KT performed the literature search, helped create the table and figures, analyzed the neuroimaging data, and wrote the manuscript. MT, KT, and KS obtained the informed consent. OS provided useful comments for the study and manuscript.

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FIGURE LEGENDS

FIGURE 1

Magnetic resonance images: (a) at baseline, (b) 18 months later, (c) 3 years later; The bilateral superior parietal lobes show slight atrophy for his age, suggesting Alzheimer's disease pattern.

FIGURE 2

[^{123}I] Iodoamphetamine single-photon emission computed tomography images at baseline; (a) axial images at baseline, (b) voxel-based analysis (using 3D-SSP software) of the images; Both (a) and (b) show hypoperfusion of Alzheimer's disease pattern, or hypoperfusion especially in the bilateral parietotemporal association areas, posterior cingulate gyri, precunei, and frontal association areas.

FIGURE 3

The images of ^{11}C-Pittsburgh compound-B positron emission tomography: (a) 18 months later, (b) 3 years later; Pathologic amyloid β accumulation is observed in the medial occipital lobes and striatums, and widespread in the gray matter. The images of both (a) and (b) show similar degree of pathologic amyloid β accumulation.

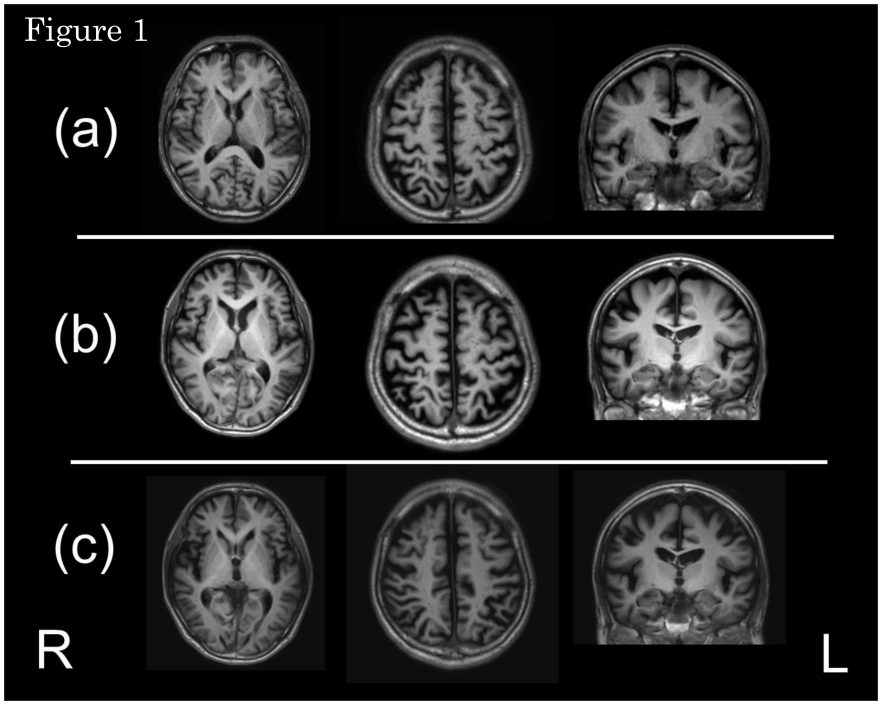
FIGURE 4

The ^{18}F-THK5351 positron emission tomography images: (a) 18 months later, (b) 3 years later; Abnormal accumulation of pathologic tau protein is shown in the bilateral medial temporal lobes, parietotemporal association areas, frontal association areas, posterior cingulate gyri and precunei. The images in (b) shows a little progression of pathologic tau protein compared to those in (a).

TABLE 1 Neuropsychological Evaluations

	Baseline	1 year later	18 months later	2 years later	3 years later
MMSE	28/30	24/30	23/30	27/30	25/30
Delayed recall	3/3	3/3	2/3	3/3	3/3
ADAS-cog	6/70	15/70	6.6/70	8.4/70	13.7/70
CDT	N/A	13/15	N/A	14/15	13/15
WMS-R					
Logical memoryI	N/A	15/50	18/50	19/50	16/50
Logical memoryII	N/A	11/50	12/50	12/50	12/50
FAB	N/A	8/18	15/18	13/18	12/18
WAIS-III					
Digit span forward	N/A	9/16	N/A	9/16	10/16
Digit span backward	N/A	5/14	N/A	4/14	5/14
ROCFT					
Copy	N/A	36/36	N/A	36/36	34/36
Delayed recall	N/A	15/36	N/A	10/36	11/36
JART	N/A	41/50	N/A	40/50	37/50

ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale Japanese version; CDR, clock drawing test; FAB, frontal assessment battery; JART, Japanese Reading Test; MMSE, Mini-Mental State Examination; ROCFT, Rey-Osterreith Complex Figure Test; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; WMS-R, Wechsler Memory Scale-Revised.



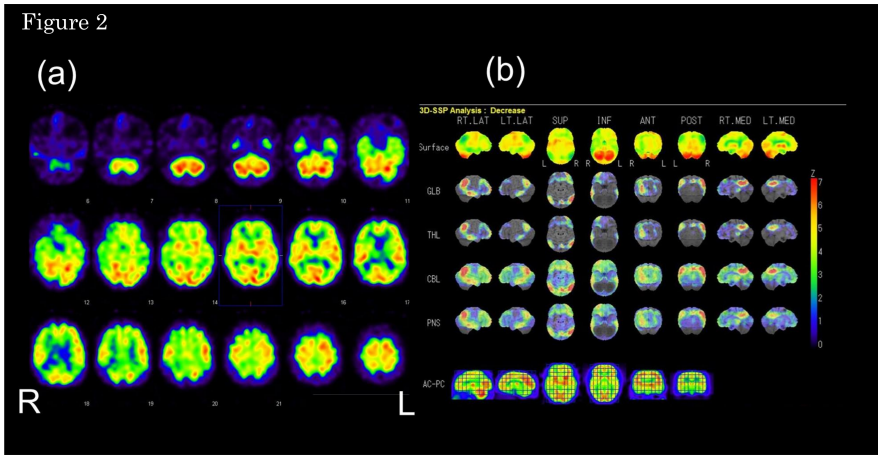


Figure 3

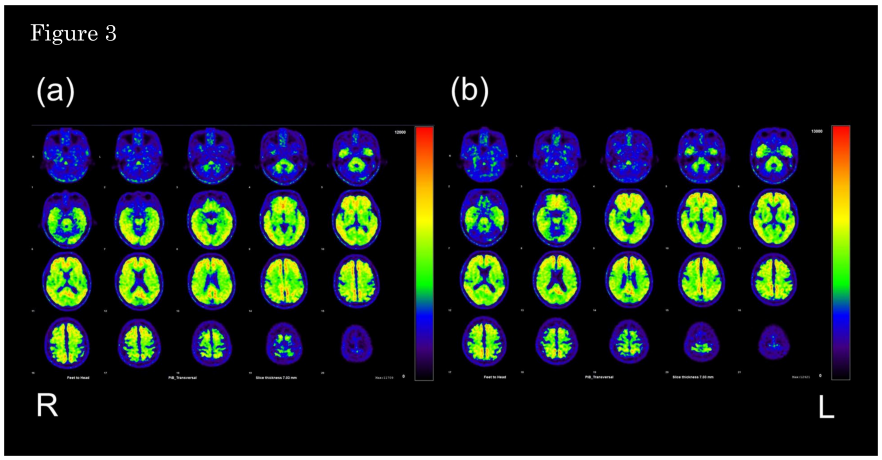


Figure 4