Thymoma Removal Improved Cognitive Function in a Patient with Alzheimer disease: A Case Report

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Abstract

Purpose: Alzheimer disease (AD) is an irreversible neurodegenerative disease that causes progressive cognitive decline. Co-existing thymoma should be considered when rapid deterioration of cognition was noted in AD patients and removal of thymoma may improve cognition in AD.

Case report: We report a 72-year-old woman with initial complaints of memory impairment for 2 years. After detailed history taking, neuropsychological tests, brain magnetic resonance imaging, and positive amyloid positron emission tomography, she was diagnosed as having dementia of the Alzheimer type. At the time of diagnosis, her dementia condition was mild (clinical dementia rating [CDR] = 1, CDR sum of boxes [CDR-sb] = 4.5, Mini-Mental State Examination (MMSE) = 21/30). She needed moderate assistance in performing daily life activities. One year after AD diagnosis, her condition deteriorated drastically, and she experienced frequent falls and severe weakness apart from cognitive symptoms. Concurrent myasthenia gravis (MG) with thymoma was found later, and thymectomy was performed. Her symptoms related to MG alleviated after the operation. Notably, her cognitive symptoms also improved 4 months after the operation, and her dementia reversed to mild cognitive impairment.

Conclusion: Although the role of neuroinflammation in AD has been widely discussed, it remains elusive. Removal of the co-existing thymoma not only alleviated the patient's MG symptoms but also improved her cognitive performance. We supposed that this effect may have been a direct result of the decrease in acetylcholine receptor antibody or reduction in the degree of neuroinflammation.

Keywords: Alzheimer disease, thymoma, neuroinflammation, central cholinergic effects, acetylcholine receptor antibody.

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BACKGROUND

Thymoma is a rare epithelial tumor of the thymus gland with an estimated incidence of 0.13–0.32 per 100,000 person-years, and it commonly manifests at the age of 40–60 years [(1)]. Typically, thymoma is asymptomatic

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and usually detected during health examinations. However, thymoma may be associated with various paraneoplastic syndromes that are usually autoimmune disorders related to T-cell dysregulation. Multiple systems such as the hematological, rheumatological, endocrine, cutaneous, and nervous systems are involved in the pathophysiology of these paraneoplastic syndromes. These syndromes may have various clinical manifestations such as myasthenia gravis (MG), dysautonomia, limbic encephalitis, myositis, pure red-cell aplasia, hypo-g-globulinaemia, glomerulonephritis, and lupus erythematosus [(2)]. Among these, MG is the most common. Most symptoms of MG are a result of the effect of autoantibodies against nicotinic acetylcholine receptor (nAChR) on the neuromuscular junctions. Alzheimer disease (AD) is an irreversible neurodegenerative disorder, with b amyloid plaques and hyperphosphorylated tau protein as the hallmarks of neuropathologic findings. As the disease progresses, the accumulation of b amyloids may reduce the amount of acetylcholine (Ach) in the brain. Currently, the major hypothesis explaining this phenomenon is the death of basal forebrain neurons responsible for ACh production and projections [(3)]. Therefore, medications aimed at increasing ACh levels in the brain are the primary pharmacological treatment option for AD.

The paraneoplastic symptoms of thymoma and cognitive symptoms of AD are both related to ACh deficits in the nervous system. In a previous case report [(4)] on a similar condition (thymoma with worsening cognitive function), the final diagnosis was reported as paraneoplastic encephalitis. In the present case, there was no conscious disturbance, seizure activities as previous case report. Notably, after thymoma removal, the cognitive and behavioral symptoms in our patient were not only reversed but also improved (from mild dementia to mild cognitive impairment [MCI]).

CASE PRESENTATION

A 72-year-old woman presented with a medical history of type 2 diabetes mellitus for more than 10 years with regular follow-up and no other health problems. She experienced memory problems for two years. She visited our memory clinic since July, 2019. At that time, she reported always forgetting her doctor appointments and asking questions repeatedly. Her family noticed her having difficulty in performing daily activities and therefore brought her to our memory clinic. Neuropsychological tests; brain MRI; and serum tests including those for thyroid function, neurosyphilis, vitamin B12/folic acid, and renal/hepatic function were conducted to rule out reversible causes of dementia. Except for poor short-term memory and mild hippocampal atrophy, all other test results were normal. Because AD was highly suspected, amyloid positron emission tomography (PET) was arranged, the results of which were positive and revealed diffuse amyloid deposition (Fig. 1) and was diagnosed AD. Since the diagnosis, she was regularly followed up in our memory clinic and received acetylcholinesterase inhibitor for AD treatment.

In early 2020, her family noticed a difference in her behavior. First, her memory problems worsened, and she began to forget to take her daily medications. Routine blood tests in our clinic revealed several episodes of high

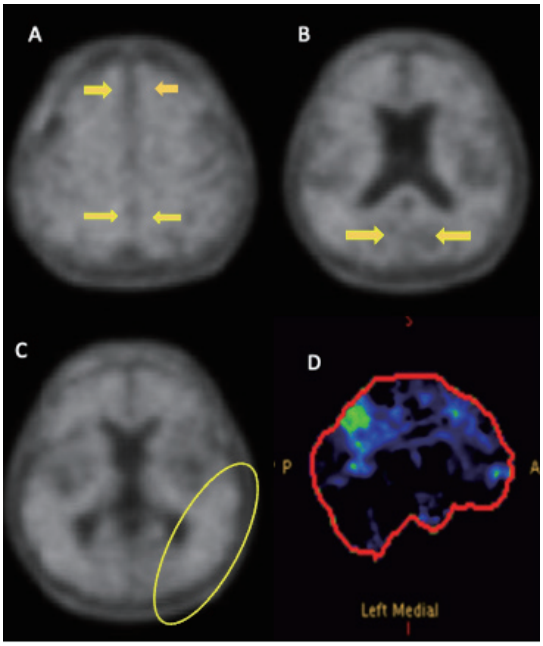

Figure 1. Amyloid positron emission tomography with florbetaben as tracer revealed diffuse amyloid deposition. (A) (B) "Kissing hemisphere" sign in the parietal and occipital lobes. (C) Loss of distinction between gray and white matter in the temporal lobe (loss of "temporal ridge" sign). (D) Early-phase perfusion scan showed hypoperfusion over the left parietal lobe (precuneus).

blood sugar. Second, she became weaker and could no longer exercise daily. At times, she spent all day in bed and refused to do anything. She also had problems with maintaining self-hygiene and started using adult diapers. She also experienced several fainting episodes. Moreover, when she did participate in family activities, her family noticed that her voice was weak and that she could not raise her head properly. Because of her increasing frequency of falls and ER visits, she was finally admitted to the hospital in May 2020 for a detailed examination. In the hospital, bilateral ptosis with diurnal change was also observed. However, no convulsions, fever, or delirium were found. Because MG was highly suspected, AChR Ab and repetitive nerve stimulation tests were conducted. And AChR Ab level disclosed 240.5 nmol/L (normal value, <0.5). Furthermore, brain MRI with contrast was arranged to rule out organic brain lesion and paraneoplastic encephalitis (Fig.2), and the results revealed no organic lesions. A subsequent chest CT with contrast revealed a thymoma located in the anterior mediastinum. Thoracoscopic thymectomy (video-assisted thoracoscopic surgery [VATS]) was performed in July 2020.

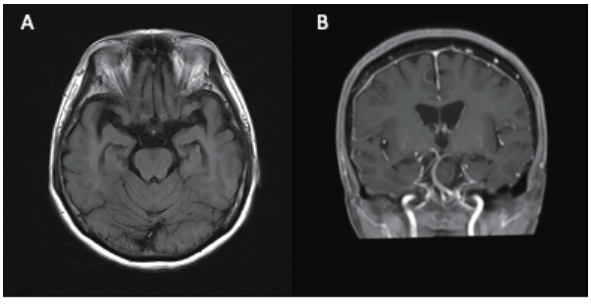

Figure 2. (A) Normal axial T2-weighted fluid attenuated inversion recovery (T2 FLAIR) sequence image of the bilateral temporal lobe (B) Coronal contrast T1-weighted brain image revealed no hyperintense or contrast-enhanced lesion

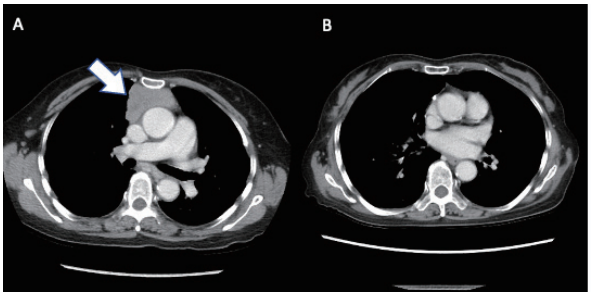

Figure 3. Initial chest computed tomography (CT) showing a 5.5 × 4.5 × 3.5 cm^3 thymoma over the anterior mediastinum (arrow). (B) Follow-up chest CT after thymectomy.

After complete removal of her thymoma (Fig. 3), not only symptoms related to MG (dropping head, ptosis, and general weakness) but also cognitive and behavioral symptoms drastically improved. Four months after thymoma removal, her weakness was alleviated, and her general cognition considerably improved (Table 1). Although she still has mild memory problems, she is currently able to live independently and perform most daily activities without assistance. In brief, her clinical condition reversed from mild dementia (clinical dementia rating [CDR] = 1, CDR sum of boxes [CDR-sb] = 4.5) to MCI (CDR = 0.5, CDR-sb = 2).

DISCUSSION

The cognitive function of most patients with AD deteriorates rapidly after a major operation, infection, a fall, cerebrovascular accidents, or other clinical conditions. In the present case, the patient not only recovered from thymectomy but her cognitive status also improved 4 months later. In our patient, the improvement in cognition was also highly correlated with the reduction of AChR Ab levels (Table 1).

In addition to the nAChR antibody, thymoma produces other synaptic antibodies including the ganglionic ACh receptor, voltage-gated Kv1 potassium channel, g-aminobutyric acid-A receptor, glycine receptor, leucine-rich glioma inactivated 1 receptor, and glutamate receptor antibodies [5,6]. These autoantibodies also contribute to various neurologic manifestations other than MG. Moreover, limbic encephalitis is one of the most common paraneoplastic syndromes of thymoma. The exact mechanism underlying cognitive impairment in patients with MG remains unclear. Central cholinergic deficit is one of the most plausible mechanisms, and several studies have supported this hypothesis [7-9]. Previous data have also identified AChR antibodies and abnormal immunoglobulin bands in the CSF of patients with MG, demonstrating the involvement of the central cholinergic system [10]. Cognitive improvement after plasma exchange (PE) in MG patients has also been reported [8]. A recent study

proved the involvement of the central cholinergic system in patients with MG by measuring their pupillometric indices [11]. These lines of evidence support the possibility that AChR antibodies can pass through the blood–brain barrier (BBB). However, some studies have reported conflicting results that do not support the involvement of the central cholinergic system in MG [12,13]. The transport of antibodies to the brain is restricted by the BBB in healthy persons. However, systemic infection or inflammatory disorders may alter this condition. This finding can explain why some patients with MG have central cholinergic deficits while others do not. In our patient, AD increased the permeability of the BBB to antibody transportation [14], and neuroinflammation caused by thymoma exacerbated the outcome.

Another condition that can explain the findings in this case is neuroinflammation. Neuroinflammation plays a crucial role in AD [15]. Typically, neuroinflammation associated with AD is mostly restricted to the central nervous system (CNS) [16,17]. The cells that contribute the most to neuroinflammation are microglia and astrocytes. The activation of microglia and astrocytes is regulated by several mechanisms and pathways such as ion channel regulation by neurotransmitters (e.g., Ach), epigenetics, autophagy, immune cell regulation by microRNA, and other unknown mechanisms [18]. In animal models, many studies have demonstrated the anti-inflammatory effect of ACh through the inhibition of release of inflammatory cytokines, especially TNF-, IL-1b, and IL-6, acting on a7 nAChR on microglia and astrocytes [19]. In a notable animal study [20], systemic inflammation was demonstrated to cause neuroinflammation in the CNS and be related to amyloid accumulation through a peripheral injection of a specific α7 nAChR Ab. Subsequently, central α7 nAChR levels decreased, IL-6 levels increased, and glial fibrillary acidic protein-positive astrocytes were found. Later, neuroinflammation and b-amyloid accumulation were detected. Ach also mediates anti-inflammatory and neuroprotective actions through the activation of the nuclear factor erythroid 2-related factor 2 pathway on microglia and astrocytes through α7nAChRs, resulting in antioxidant properties [21]. Because of its anti-neuroinflammatory and neuroprotective effects, ACh is currently used in the symptomatic treatment of AD [22].

In our patient, thymoma produced systemic inflammatory responses through the upregulation of several cytokines and chemokines. These inflammatory responses facilitated the penetration of peripheral nAChR antibodies into the CNS, which further aggravated central cholinergic deficits. In addition, AD itself may have caused a systemic immunosuppressed state that further reduced the clearance of amyloid plaques in the brain. This is consistent with the finding of a previous study [23] in which AD pathology was attenuated in mice with the amyloid precursor protein gene deleted by boosting the immune system. The systemic inflammation caused by thymoma in our patient aggravated neuroinflammation. Because thymoma is not a rapidly growing tumor, the

Table 1. Cognitive test results and AChR Ab levels before and after thymectomy

	2019/7	2020/5	2020/11 (after OP)	2021/11
AChR Ab	NA	240.5	16	19.4
MMSE	22	21	24	24
CASI	69	69	73	67
CDR	1	1	0.5	0.5
CDR-SB	4.5	6	2	4
Memory	1	2	1	1
Orientation	1	1	0.5	0.5
Judgment	1	0.5	0.5	1
Community affair	1	0.5	0	0.5
Home & Hobbies	0.5	1	0	0
Personal care	0	1	0	1

Note: AChR Ab: acetylcholine receptor antibodies (nmol/L), MMSE: Mini-Mental State Examination, CASI: Cognitive Abilities Screening Instrument, CDR: clinical dementia rating, CDR-SB: clinical dementia rating sum of box

initial presentation of dementia may have been partly caused by thymoma.

The Alzheimer Management by Albumin Replacement (AMBAR) clinical trial reported positive outcomes of AD treatment with routine PE[24]. The study proved that all patients with mild to moderate AD treated with PE exhibited less decline in CDR-sb and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scores. The trial primarily aimed to remove albumin-bound amyloid beta (Aβ) protein from peripheral blood such that more CSF Aβ protein may be transmitted to the plasma and less amyloid plaque will accumulate in the brain. However, PE is also a method of removing cytokines or antibodies from plasma and is used to treat in many immune-mediated diseases. The successful results reported by the AMBAR study might be attributable to the removal of certain neurotoxins and antibodies from the blood of AD patients, thus partly reversing neuroinflammation. In fact, specific nAChR autoantibodies have been proven to be produced in response to some common infections and be present in the peripheral blood of healthy individuals [25]. An intact BBB restricts these antibodies from entering the CNS. However, the integrity of the BBB may be damaged in specific conditions such as AD, aging, or systemic inflammation; as a result of these conditions, these autoantibodies enter the CNS and exacerbate neuroinflammation.

CONCLUSION

In our case, thymoma removal directly reduced the amount of ACh receptor antibodies and possibly alleviated central cholinergic effects. Most importantly, thymectomy itself also reduced the degree of neuroinflammation. Although rare, thymoma should be considered in the differential diagnosis of rapid deterioration in patients with AD. Our case also corresponds to a recent trial of PE for AD treatment. Treatments that may increase the amount of ACh or reduce the neuroinflammation are worth further investigation.

Limitations

In this case report, we didn't perform CSF analysis for confirming the status of nAChR antibodies or neuroinflammation. In the future, CSF analysis should be done for complete study.

Abbreviations

AChEI: Anticholinergic-esterase inhibitor
AChR Ab: Acetylcholine receptor antibody
AD: Alzheimer's disease
AMBAR: Alzheimer Management by albumin replacement
BBB: Blood brain barrier
CDR-sb: Clinical dementia rating-sum of box
CNS: Central nervous system
CSF: Cerebrospinal fluid
CT: Computed tomography
DAT: Dementia of Alzheimer type
ER: Emergency department
GFAP: Glial fibrillary acidic protein
MCI: Mild cognitive impairment
MG: Myasthenia gravis
MMSE: Mini mental state examination
MRI: Magnetic resonance imaging
Nrf2: Nuclear factor erythroid 2-related factor 2
PE: Plasma exchange
PET: positron emission tomography
VATS: Video-assisted thoracoscopic surgery

Ethics approval and consent to participate

Institutional review board of Cardinal Tien Hospital, Taipei, Taiwan, approved the study. Written informed consent was obtained from the patient for publication of this case report.

Consent for publication

Signed informed consent was obtained from the patient and patient's family for publication of this case report and accompanying neuroimages and data.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due on our policy statement of sharing clinical data only on request but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contribution

YCL and LHL contributed to writing and revised the manuscripts. PCY and YMF contributed to interpreting the research data and neuroimages. All authors read and approved final manuscript.

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