

# Paraneoplastic Limbic Encephalitis Associated with Adenocarcinoma of Lung

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## Abstract-

**Purpose:** Paraneoplastic limbic encephalitis (PLE) is a rare, immune-mediated entity. We present an unusual case of a patient who has double cancers and two different paraneoplastic neurological syndromes.

**Case Report:** A 58-year-old gentleman has histories of adenocarcinoma of lung and malignant thymoma associated with myasthenia gravis, which underwent surgery and chemotherapy 3 years ago. This time, he presented to our ward with rapidly progressive memory decline and myoclonic jerks in his limbs for two weeks. Magnetic resonance imaging (MRI) of brain showed increased signal intensity over bilateral mesial temporal regions on T2 Fluid Attenuated Inversion Recover (FLAIR) series. Chest computed tomography showed cancer recurrence. He received steroid pulse therapy firstly and right lung lower lobe lobectomy later. Pathology report of the tumor was recurrent adenocarcinoma. After the immunotherapy and tumor resection, his mentality improved gradually. Six months later, brain MRI showed resolution of bilateral temporal hyperintensity with residual mesial temporal atrophy.

**Conclusion:** From our case, we would like to emphasize that paraneoplastic limbic encephalitis should be considered among the differential diagnosis of rapidly progressive dementia associated with myoclonus, along with other neurodegenerative diseases. Depending on its underlying malignancy, the cognitive impairment may be substantially reversible, despite atrophy of mesial temporal lobes.

**Key Words:** adenocarcinoma of lung; paraneoplastic limbic encephalitis; paraneoplastic neurological syndromes; rapidly progressive dementia

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## INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are rare

presentations of malignancy, occurring in less than 1% of cancer patients<sup>(1)</sup>, but prevalence varies according to cancer type. Within the scope of PNS, the more common

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syndromes are paraneoplastic cerebellar degeneration, paraneoplastic limbic encephalitis (PLE), sensory neuronopathy, opsoclonus-myoclonus syndrome, Lambert-Eaton myasthenic syndrome and myasthenia gravis. The more commonly associated cancers of paraneoplastic syndromes are neuroendocrine tumors (e.g., small-cell lung cancer and neuroblastoma), germ-cell tumors, ovarian cancer, breast cancer, thymoma and lymphoma<sup>(2)</sup>. Here, we present a patient who has double cancers and two different paraneoplastic neurological disorders.

## CASE REPORT

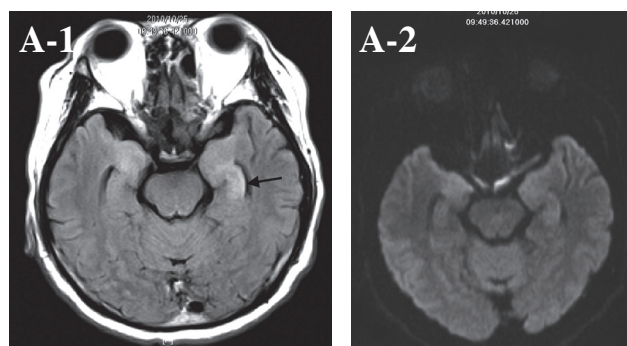
A 54-year-old gentleman has the history of double cancers, malignant thymoma stage IVa with generalized myasthenia gravis and lung adenocarcinoma stage pT2aN0M0, which underwent surgical removal and chemotherapy 3 years prior to admission (PTA). He took low dose oral steroid regularly for myasthenia gravis (MG), and his symptoms of ptosis and general weakness were under good control, so he continued running his own machine factory and was independent in activities of daily life.

He had acute onset non-fluctuating memory impairment one month PTA, in both aspects of recent memory and some remote memory. He also had intermittent right limbs jerks at night during sleep. When he was admitted into our ward, the initial neurological examination showed relatively normal mental status except poor short-term memory (3-item delayed recall test scored 0 out of 3). There were no other focal neurological deficits. Mini-mental status examination (MMSE)<sup>(3)</sup> scored 26/30. Blood tests including complete blood cell count, biochemistry profile, tumor markers (alpha-fetoprotein, CA-199, CEA, PSA), endocrine factors (thyroid-stimulating hormone, free T4, cortisol, vit B12/folic acid), autoimmune profile (anti-thyroid peroxidase antibody, thyroglobulin antibody, antinuclear antibody, rheumatoid factors, extractable nuclear antibody (ENA)), viral antibody titers (HSV-IgM, VZV-IgM, HIV) were negative or within normal limits. The initial brain magnetic resonance imaging (MRI) was negative for any significant parenchymal or vascular lesions. The cerebrospinal fluid (CSF) analysis revealed grossly normal findings with WBC 3/CUMM, RBC 3/CUMM, protein 26 mg/dL,

glucose 71 mg/dL, negative oligoclonal band, but elevated IgG index (0.66).

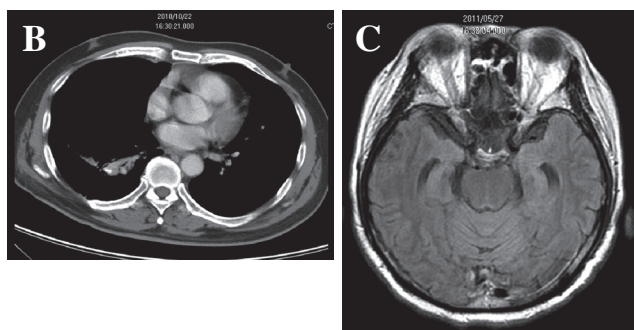
During hospitalization, increasing frequency of myoclonic jerks over his left limbs occurred, which was associated with retrograde amnesia of what he was doing before the jerk and transient post-ictal confusion as well. Despite electroencephalography (EEG) failed to show any epileptiform discharges, valproic acid was prescribed under the impression of complex partial seizure. As his cognitive function deteriorated further, including orientation, memory, visuospatial function and executive function, he became partially dependant on his wife for daily life activities. The follow-up MMSE 16 days later scored 15/30 and Montreal cognitive assessment (MoCA)<sup>(4,5)</sup> scored 10/30.

The follow-up Brain MRI 3 weeks after admission showed faint hyperintensity over bilateral mesial temporal region on T2 Fluid Attenuated Inversion Recover (FLAIR) image and diffusion weighted image (DWI) (Figure A-1 and A-2). Under the impression of limbic encephalitis, he received a course of methylprednisolone pulse therapy at dosage of 750mg/day for 5 days. For survey of suspected paraneoplastic limbic encephalitis (PLE), chest computerized tomography was done, and it revealed tumor recurrence at the right lower lobe, near the previous resection site (Figure B). Five weeks from the date of admission, he received a complete right lower



**Figure A-1.** Brain MRI T2-FLAIR series showed faint hyperintensity over bilateral mesial temporal lobes, left side more than right side (arrow)

**Figure A-2.** Brain MRI DWI series also showed faint hyperintensity over bilateral mesial temporal lobes.



**Figure B.** Chest computerized tomography for malignancy survey, which revealed tumor recurrence near the surgical clips from the prior lung surgery.

**Figure C.** Follow-up brain MRI 7 months later showed complete resolution of the hyperintensities, but residual mesial temporal atrophy.

lobe lobectomy with extended lymph nodes dissection. Pathology was recurrent adenocarcinoma, 2cm in size, moderately to poorly differentiated, around previous operation site, rPT1aNOMx.

After the immunotherapy and tumor resection, he was regularly followed up at neurology outpatient department. Two months later, his MMSE score improved to 25/30. Follow-up Brain MRI 3 months later still revealed mild bilateral mesial temporal hyperintensity on FLAIR image. Six months later, MMSE scored 30/30 and MoCA scored 27/30, and follow-up Brain MRI showed complete resolution of mesial temporal hyperintensity, but advanced to bilateral mesial temporal atrophy (Figure C).

## DISCUSSION

In this case, the patient had rapidly progressive, persistent, non-fluctuating memory impairment, associated with myoclonic jerks of his limbs. Among the differential diagnoses of rapidly progressive dementia, Creutzfeldt-Jakob disease should be firstly considered, especially when the dementia and myoclonus co-occurs<sup>(6)</sup>. Neurodegenerative dementias such as Alzheimer's dementia, dementia of Lewy bodies and corticobasal degeneration can present in a fulminant, rapidly progressive fashion<sup>(6,7)</sup>. They manifest with myoclonus in up to 50%, 15% and 50% respectively<sup>(8)</sup>, but their occurrence is typically in older age. Besides,

limbic encephalitis is another differential diagnosis, either of infectious or inflammatory etiology. Limbic encephalitis is known to present with rapidly progressive short-term memory deficits, psychiatric symptoms, and seizures<sup>(9)</sup>. Since our patient has the history of malignancy, etiologies of cancer-associated cognitive impairment, such as brain parenchymal or leptomeningeal metastases, hypercoagulability associated vascular lesions, immunosuppression-related infections and paraneoplastic limbic encephalitis must be considered<sup>(10)</sup>. In our case, the brain images, CSF studies and blood tests have excluded most of these onco-neurological complications and supported the diagnosis of PLE.

The diagnostic criteria of PLE was defined by Gultekin and associates, which requires all four of the following: 1) a compatible clinical picture of limbic system involvement; 2) an interval of < 4 years between onset of neurological symptoms and cancer diagnosis; 3) exclusion of other neuro-oncological complications; 4) at least one of the following: i. CSF with inflammatory changes (pleocytosis, intrathecal immunoglobulin synthesis and oligoclonal bands) but negative cytology; ii. MRI FLAIR or T2 temporal lobe hyperintensities; iii. EEG showing epileptic or slow activity in temporal lobes<sup>(11)</sup>. An additional criteria is identification of well characterized antineuronal antibodies such as anti-Hu, Yo, CV2/CRMP5, Ri, Ma2, or amphiphysin<sup>(12)</sup>. An early diagnosis is sometimes difficult to make because the clinical markers are often negative. Up to 50% of patients do not have the classical paraneoplastic or antineuronal antibodies in serum or CSF. Typical brain MRI findings and inflammatory abnormalities in CSF study are both found only in approximately 60% of PLE patients. Additionally, in 60~70% of the patients, the neurological symptoms preceded the diagnosis of cancer<sup>(11)</sup>. Despite our presenting case eventually did meet all the criteria of PLE, he had normal brain MRI and EEG at the initial examination. It was until three weeks later, his brain MRI showed increased signal over bilateral limbic area. Therefore, close follow-up studies sometimes are critical for the patients presenting with rapidly progressive dementia. Even more importantly, a vigorous search for associated tumor is indicated. Despite unavailability of antineuronal antibodies assessment in our hospital, his clinical response to surgical resection of recurrent tumor

further supported of the diagnosis of PLE.

Recently, the importance of classifying paraneoplastic antibodies into antineuronal (intracellular antigens) and antineuropil (cell membrane antigens) antibodies was emphasized, because now we know the response to tumor treatment and immunomodulations was much better in those without classical antineuronal antibodies<sup>(2)</sup>. In addition, few literatures have discussed the serial MRIs of limbic encephalitis and the correlation with treatment response. In one case series, Urbach H. et al analyzed the serial brain MRI scan changes of twenty limbic encephalitis patients. It concludes that mesial temporal swelling and hyperintense signals on T2-weighted or FLAIR sequences of the acute stage would persist up to months or years, then progress to mesial temporal atrophy in most cases<sup>(13)</sup>. However, the clinical outcomes of the 20 patients were not presented. Another case series of seven limbic encephalitis patients reported six patients with antineuropil antibodies had dramatic clinical and neuroimaging responses to immunotherapy and tumor therapy; the MRI hyperintensities resolved without evolution to atrophy. One out of the seven patients had antineuronal antibodies and his MRI scans showed progressive atrophy of hippocampi, which lead to progressive deterioration and death<sup>(14)</sup>. Whereas from our patient, we observed that substantial reversibility of cognitive impairment was possible despite mesial temporal atrophy occurring after the active inflammation. Furthermore, changes in the brain MRI are much delayed after clinical improvement or deterioration, so brain MRI follow-up is less informative about prognosis of limbic encephalitis than the clinical picture.

In conclusion, PLE should be a differential diagnosis of rapidly progressive dementia associated with myoclonus. Repeating neuroimaging, CSF and EEG studies, as well as a vigorous search for underlying malignancies, are necessary for accurate diagnosis. Sometimes with adequate treatment, PLE could be a reversible dementia.

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