Clinical characteristics of patients with motor neuron disease and concurrent tumors

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To the Editor: Motor neuron disease (MND) is a kind of progressive, fatal neurodegenerative disease involving the upper and lower motor neurons and the pyramidal tract. Currently, the etiology of MND remains unknown, and there are limited treatment strategies. Paraneoplastic syndrome (PNS) is a rare form of MND-mimic syndrome. There have been reports of MND-like clinical symptoms in patients with different types of cancer, including breast cancer, lung cancer, and lymphoma. Epidemiological studies have drawn different conclusions, some have suggested that there is no relation between site-specific cancers and the risk of incident amyotrophic lateral sclerosis (ALS), while others have found that the overall risk of cancer of any site is significantly reduced in cases with ALS.1 However, the prevalence of tumors in Chinese MND patients and the characteristics of patients with MND concomitant tumors are unclear.

From January 2010 to December 2016, 1751 patients visited the Peking University Third Hospital (PUTH) and were diagnosed with MND. According to the revised El Escorial criteria, the diagnostic grades of these patients were possible, lab-supported probable, probable, or definite. Our patients were followed up every 3 months by either phone or face-to-face interview. The endpoint event was defined as death or invasive mechanical ventilation. This study was approved by the Ethics Committee of PUTH, Beijing, China. The study group obtained written informed consent from each patient before they participated in the study.

Among 1751 MND patients, 28 (1.6%) had concurrent tumors, the proportion is lower than that of 8.7% or 10.1% reported in the literature.2 Therefore, we considered the possibility of the missed diagnosis of tumors in our patients. The most common type of malignancy was lung cancer (n = 8, one case of small cell lung cancer, three of lung adenocarcinoma, and four of unknown pathological type), followed by lymphoma (n = 3, one case of Hodgkin lymphoma, one of mantle cell lymphoma, and one of intestinal lymphoma), breast cancer (n = 3), thyroid cancer (n = 2), esophageal cancer (n = 2), and gastric cancer (n = 2). One patient had concurrent esophageal cancer and kidney cancer. This result of lung cancer, breast cancer, and lymphoma as the most common types in MND patients is consistent with the results reported in the literature.3 Thyroid cancer has been rarely reported, Liu et al4 reported one paraneoplastic MND with thyroid cancer. However, current studies mostly focus on case reports, and the number of cases is small, the specific mechanism remains unclear. Whether MND is associated with abnormal autoimmunity caused by molecular mimicry between tumor-associated antigens and neuron-associated antigens still requires further investigation. A total of 64.3% (n=18) of patients were diagnosed with tumors after the diagnosis of MND, and the median time between the diagnosis of MND and tumors was 20 (interquartile range [IQR] = 64) months.

In addition to motor symptoms, four (14.3%) patients had a sensory impairment, including one with severe pain, four (14.3%) had a cognitive or affective impairment, and two (7.1%) had bowel or bladder dysfunction. In a review by Mele et al,5 the clinical features of 29 patients with paraneoplastic ALS were characteristics of combined non-motor symptoms such as sensory neuronopathy, suggesting that tumors may extensively impair motor, sensory, and advanced cortical functions. MND is currently considered a multisystem disease with extra-motor involvement. It has been reported that approximately 15% to 45% of MND patients have executive and behavioral disorders of varying degrees at different stages of the disease.6 Patients in the study mainly manifested as memory loss, anxiety, and depression. In addition, it has

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been concluded that more than 60% of MND patients with sensory symptoms, including paresthesia and pain; and autonomic dysfunction [6] occurs in about one-third of patients, the most common autonomic symptoms are sweating dysfunction, urinary urgency, and constipation. Sensory and autonomic symptoms, which may arise as a result of musculoskeletal origin, psychological factors, or deposition of TAR DNA-binding protein 43, are common but modest. In clinical practice, for patients with clinical manifestations that do not conform to typical symptoms of MND, such as cognitive impairment incompatible with frontotemporal lobar degeneration, or severe pain, further examinations should be performed for tumor screening.

The proportion of patients who underwent lumbar puncture in our study was approximately 18%. The low positive rate of tumor markers (16.7%) and onconeuronal antibodies (5.3%) indicates that in clinical practice, especially in the outpatient department, the etiological screening of MND patients is insufficient and that the sensitivity of markers commonly used in clinical practice is low. Therefore, highly sensitive biomarkers are still needed to assist in the early diagnosis of tumors.

A total of 1723 MND patients without tumors diagnosed during the whole course of the disease, including 1092 (63.4%) males, had a mean onset age of 51.5 (standard deviation [SD] = 11.6) years, which was significantly lower than that of patients with tumors (61.9 years, SD = 9.8). Because the onset age is not comparable between the two groups and the age at onset may have an impact on lifespan, MND patients without tumors were matched to the 28 patients at a ratio of 4:1 according to sex and onset age by the propensity score matching (PSM) method. PSM is a method used to balance confounding factors between groups in observational studies, and we aimed to make confounding factors comparable between the two groups by PSM.

The last follow-up was in May 2019, and the median follow-up time for patients with tumors was 37 (IQR = 69) months. The number of patients who reached the endpoint was thirteen (46.4%), of which 11 died and two underwent a tracheotomy. Totally, three patients were lost to follow-up. The median follow-up time for patients without tumors was 25.5 (IQR = 24) months, and 55 (49.1%) patients reached the endpoint. The Kaplan-Meier curve showed that the survival time of the MND patients with tumors was significantly longer than that of the patients without tumors (P = 0.006). Analysis using a Cox proportional hazards model suggested that the diagnostic delay time, interval to the second segment, presence of tumors, and treatment of MND were factors that affected survival time. After controlling for the other factors, the survival time of the patients with tumors was still longer than that of the patients without tumors (hazard ratio: 0.216, 95% confidence interval: 0.065–0.715, P = 0.012) [Figure 1].

We suggest the following possible reasons. First, two MND patients with tumors presented with flail arm syndrome (FAS)/flail leg syndrome, and two patients met the diagnostic criteria for isolated bulbar ALS (IBALS). The symptoms of these patients are confined to a certain segment for a long time, and those patients have a good prognosis. Second, some patients stabilize after tumor-targeted therapy or immunotherapy, suggesting that tumor-induced autoimmunity, or other mechanisms, such as oxidative stress, apoptosis, and methylation, plays a partial role and that the disease course is different from that of degenerative diseases.

Among the 28 patients, one was diagnosed with definite PNS according to the diagnostic criteria by Graus, and 12 were diagnosed with possible PNS. The patient diagnosed with PNS was positive for the antibody amphiphysin in blood and negative in cerebrospinal fluid, but neurological symptoms after surgical resection of the lung cancer still deteriorated, not according with canonical PNS. Among the 12 possible PNS, nine could be diagnosed with typical ALS, and two were initially diagnosed with progressive bulbar palsy; however, according to the IBALS criteria, one patient could be diagnosed with IBALS, one patient with FAS. Three patients presented with symptoms other than...
the motor system, including cognitive and sensory impairment. The most common type of tumor was lung cancer \( (n=4) \), followed by hematologic tumors \( (n=3) \), thyroid cancer \( (n=2) \), breast cancer \( (n=1) \), prostate cancer \( (n=1) \), and gastric cancer \( (n=1) \). Only two patients showed MND symptoms after the tumors.

In conclusion, we analyzed the clinical characteristics of patients with MND and concurrent tumors, and they were different from patients with degenerative MND in terms of clinical manifestations and disease progression. Though the cases are rare, further study is necessary to elucidate the mechanisms and direct early diagnosis and treatment strategies.

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**Conflicts of interest**

None.

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