CASE REPORT

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Paraneoplastic neurological syndrome associated with onconeural autoantibodies: report of two cases

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ABSTRACT

Paraneoplastic neurological syndromes (PNS) are rare and often severe neurological complications of malignancies, significantly impacting patient prognosis and quality of life. They are characterized by a diverse range of onconeural autoantibodies, with further discoveries likely due to ongoing research. Among these, high-risk autoantibodies primarily target intracellular neural cell antigens. We present cases of lung cancer patients who developed limbic encephalitis and seizures at diagnosis, suggestive of PNS. Each case demonstrated distinct autoantibody profiles. Recognition of these potentially life-altering neurological sequelae, as paraneoplastic manifestations of malignancies, is crucial for physicians. PNS may precede primary cancer diagnosis and substantially affect patient presentation and overall outcome. We provide in detail the diagnostic work-up and available treatment options for these complex cases.

Keywords: Anti-Hu; Anti-Zic4 antibodies; Limbic encephalitis; Paraneoplastic cerebellar degeneration; Small cell lung carcinoma

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) were first recognized in the 1950s as a remote immune-mediated effect of cancer [1]. Population-based studies have shown that limbic encephalitis, cerebellar degeneration, and encephalomyelitis are the most common PNS [2]. According to the updated diagnostic criteria, autoantibody testing is central to accurate diagnosis [3]. These autoantibodies target neural cell-specific antigens ectopically expressed by tumor cells. They are typically classified based on the localization of their target molecule: intracellular or accessible for antibody binding (cell-surface or synaptic) [4]. As per the updated criteria, the in-

tracellular antigen-derived class of onconeural antibodies is considered high-risk due to its strong association with cancer. Their effect appears to be mediated via the T-cell-cytotoxic pathway [1]. While treatment of the underlying neoplasia remains the mainstay of therapy, immunosuppression is usually effective for antibodies targeting cell-surface/synaptic antigens, which are less commonly paraneoplastic [4]. This report describes two rare cases of lung cancer-related PNS with distinct autoantibody profiles. Consent was obtained from both patients' relatives.

CASE REPORTS

Case 1

A 72-year-old male patient presented with acute-onset disorientation and word-finding difficulty following excessive body activity. Neurological examination revealed no other abnormalities. His medical history included hypertension, heavy smoking (45 pack-years, quit 3 years prior), and social drinking. Additionally, a 3-month history of behavioral and mental changes, characterized by obsessive-compulsive behavior and anterograde memory disturbance, was reported. Physical examination was unremarkable, except for low-grade fever upon admission. Routine laboratory tests were normal. Brain computed tomography (CT) scan showed only microangiopathy. Lumbar puncture yielded clear cerebrospinal fluid (CSF) with normal glucose and elevated protein level (141 mg/dL, normal value <45 mg/dL). The film array detected human herpesvirus-6 DNA in both CSF and peripheral blood. Despite receiving intravenous ganciclovir, the patient's clinical condition worsened. Brain magnetic resonance imaging (MRI) revealed T2/fluid-attenuated inversion recovery hyperintensities without restriction, primarily involving the right medial temporal lobe, anterior cingulate gyrus, transhemispherical fissure, and various parts of the frontal lobes (Fig. 1), suggesting limbic encephalitis. He developed complex focal seizures that progressed to status epilepticus and required intubation and admission to the intensive care unit (ICU). A chest CT scan revealed a potential tumor in the right lung hilum. CT-guided biopsy confirmed small cell lung cancer. The paraneoplastic panel autoantibody screen in serum and CSF was positive for Hu and Zic 4 antibodies. Upon discharge from the ICU, the patient developed stereotypic movements and eventually cerebellar ataxia with significant truncal instability and inability to walk. He received intravenous and then oral corticosteroids, experiencing mild improvement in behavioral disturbances and cerebellar ataxia. Unfortunately, he was referred to oncology for chemotherapy, but died of a respiratory tract infection a month later.

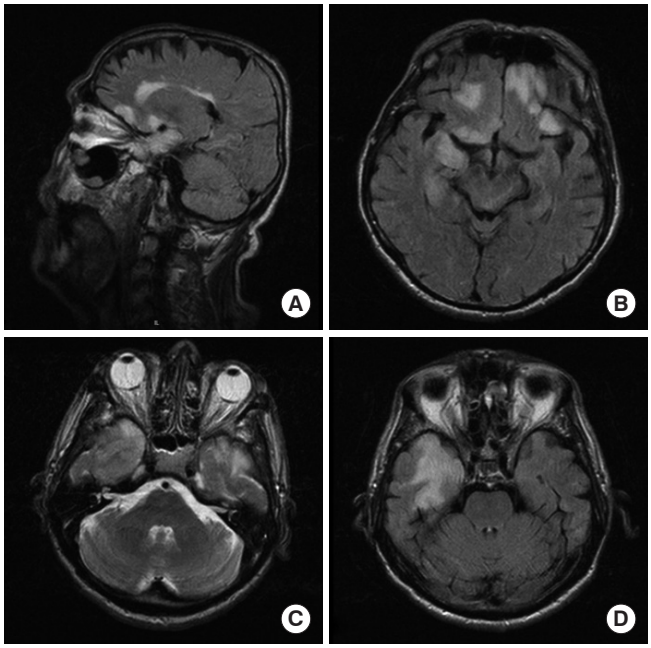

Fig. 1. (A-D) Brain magnetic resonance scan images. Enhanced magnetic resonance signal (T2/fluid-attenuated inversion recovery sequences) without the restriction of the diffusion, mainly in the right medial temporal lobe, the anterior ligament, around the transhemispherical fissure, and in various parts of the frontal lobes.

Case 2

A 79-year-old male patient presented to the Internal Medicine ward with a month-long history of intermittent fever spiking to 39.0 °C, drenching sweats, weight loss, and expectoration. Prior outpatient antibiotic treatment proved ineffective. His past medical history included depression, smoking, and alcohol abuse. Upon admission, inflammatory markers (C-reactive protein) were significantly elevated (>30 times the normal range), while procalcitonin levels remained normal. Blood and urine cultures were negative, and an extensive screen for respiratory pathogens yielded no results. Broad-spectrum antibiotics (piperacillin-tazobactam) were initiated without improvement. A chest and abdomen CT scan revealed a mass measuring 9.3 × 5.5 × 6.6 cm in the right lower lobe. The lesion abutted the posterior wall of the left atrium and pulmonary trunk, with possible esophageal infiltration evidenced by proximal dilation. No significant lymphadenopathy was observed. Esophagoscopy, however, ruled out esophageal pathology.

A purified protein derivative skin test for tuberculosis was negative. During his hospitalization, the patient developed

confusion, agitation, and later lethargy. Subsequent brain CT and MRI scans did not reveal secondary lesions or other abnormalities. Intravenous dexamethasone was administered as rescue bridging therapy, but his condition did not improve.

Lumbar puncture yielded positive findings for pleocytosis (50 cells/μL). Cytological analysis of the CSF did not identify malignant cells. An autoimmune encephalitis screen returned positive for voltage-gated potassium channel (VGKC) antibodies. Bronchoscopy was unsuccessful due to the patient becoming hypercapnic and requiring urgent intubation. He sadly passed away in the ICU 10 days later.

DISCUSSION

Neural autoantibodies targeting intracellular antigens, such as Hu (ANNA-1) and Zic 4, are considered high-risk and are almost invariably associated with malignancies [5]. Detection of these onconeural antibodies in conjunction with PNS manifestations may precede the diagnosis of malignancy by up to 5 years [2]. Hu autoantibodies, also known as antineuronal nuclear antibody-type 1, target a 35 to 40 kD protein family primarily located in the nuclei and, to a lesser extent, the cytoplasm of neurons in the central and peripheral nervous systems [6]. Zic 4 antibodies recognize zinc-finger proteins expressed in the central nervous system [7]. Population-based studies have demonstrated that lung, breast, lymphoma, gastrointestinal, ovarian, and urinary tract cancers are the most frequent malignancies associated with these antibodies.

The co-existence of Zic 4 and Hu antibodies is common and strongly linked to small cell lung cancer, suggesting shared target antigens in the tumor [7]. These antibodies are not considered directly pathogenic but act as targets for cytotoxic T-cell infiltration through cross-reactive intracellular epitopes [8]. Patients typically do not respond well to standard immunomodulatory treatments; tumor treatment remains the primary line of therapy [9]. Due to their life-threatening complications, we employed steroids as rescue bridging therapy in both cases until definitive treatment (surgical excision, chemotherapy, or radiation treatment) could be initiated. Interestingly, our second patient, who deteriorated rapidly, tested positive for VGKC autoantibodies. Recent discoveries suggest that these antibodies might not target the VGKC itself, but rather other cell-surface antigens within the VGKC complex [10]. Although the association between these antibodies and cancer is considered low, investigating the possibility of an underlying neoplasm is crucial, especially in patients with relevant clinical symptoms.

PNS can cause severe disabilities and are associated with significant morbidity. The differential diagnosis is broad. Early and accurate diagnosis is crucial, especially considering the diverse clinical features and non-specific findings in the diagnostic work-up, including radiological results. Clinical awareness is key to achieving this early diagnosis, which ultimately leads to more favorable patient outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Drafting the work or revising: PK, CK, ES, AV, SC, KP, AP.
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