Anti-amphiphysin antibody-associated paraneoplastic brainstem encephalitis with pruritus and dysphagia as the first symptoms: a case report

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Case Report

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Abstract

Anti-amphiphysin antibodies are uncommonly detected in paraneoplastic neurologic syndromes (PNS). If this happens, it is likely to present as a stiff-person syndrome (SPS). Here, we report the first case of PNS with pruritus as the first complaint, whose serum examination showed anti-amphiphysin antibodies IG+++, and the lung puncture confirmed small-cell lung cancer (SCLC). During the progression of the disease, the patient developed dysphagia and anxiety. With chemotherapy and paroxetine 20mg/d, his symptoms significantly improved. This case report emphasizes that clinicians should consider diagnoses other than anxiety states or esophageal cancer in a patient with pruritus and dysphagia, such as PNS.

1. Background

Paraneoplastic neurologic syndromes (PNS) are a group of clinical syndromes in which the nervous system is involved due to the distal effects of the tumor. The primary mechanism is now thought to be immune-mediated cross-reactivity between tumor antigens and normal neuronal tissues rather than direct invasion, compression, or metastasis of the tumor (1). The target antigens that are attacked during the immune response are divided into two main groups. One is nuclear or cytoplasmic proteins such as Hu, Yo, and Ma2. The other is intracellular synaptic proteins including amphiphysin and 65 kDa glutamic acid decarboxylase (GAD65)(2). Our case report first describes paraneoplastic brainstem encephalitis as a result of anti-amphiphysin antibodies with pruritus and dysphagia as its initial symptoms.

2. Case Description

A 58-year-old man visited the Fourth Hospital of Hebei Medical University (Hebei Provincial Cancer Hospital), in August 2022, with a 2-month history of dizziness and blurred vision. One month ago, he had dysphagia and scattered red herpes on the craniofacial region. At the local hospital, he was diagnosed with lung occupancy, while the pathology only indicated inflammatory and necrotic tissue. He was later seen at another hospital and underwent two cranial enhancement MRIs. Neither of them showed any meaningful imaging signs. In the outer basal segment of the right lung lower lobe, PET-CT revealed small occupancies with hypermetabolism. The neuron-specific enolase (NSE) level was moderately elevated, and the paraneoplastic-related antibody profile in serum revealed anti-Amphiphysin antibodies IG+++.

Half a month ago, the dysphagia worsened leading to the placement of a gastric tube for enteral nutrition. For further clarification of the diagnosis, he came to our hospital. He had a history of smoking for more than 40 years but no history of drinking.

On admission, the Watian water swallowing test was grade 5, with scattered red herpes on the forehead and the left side of the head. Other neurological facial examinations were normal. The blood routine and biochemical examinations did not reveal any abnormalities. No cancer cells were found in the cerebrospinal fluid (CSF). The routine and biochemical examinations of CSF: protein ±; erythrocyte count: 29 x 10^6 /L; leukocyte count: 3 x 10^6 /L. The chest puncture was performed on August 10, 2022, and the pathology showed small-cell lung cancer. In addition, he completed other examinations:
Electromyography suggested peripheral nerve damage. Repetitive transcranial magnetic stimulation (rTMS): low frequency, no decrement, high frequency, and no increment. The neostigmine test was negative. As for the herpes, herpes zoster was diagnosed based on morphology and antiviral medication was used in the treatment. Eventually, the patient was thus clearly diagnosed with small cell lung cancer, paraneoplastic syndrome and herpes zoster.

For the treatment of lung cancer, etoposide 0.1 g + cisplatin 40 mg was given. After chemotherapy, the patient’s symptoms were dramatically relieved: on the first day, he could drink; on the second day, he could eat as usual, and the gastric tube was removed. Gradually, the herpes were also reduced. Upon discharge, the Watian water swallowing test fell to grade 1. The herpes had disappeared entirely.

Subsequently, the patient came to our hospital for chemotherapy every 21 days. After the third cycle, he suffered from severe pruritus around the left corner of the mouth and lower extremities (especially proximal and dorsal). It was insect-like, and the patient was unable to wear a mask, and his urination intervals were shortened to every half hour due to the irritation around his urethra. His quality of life was seriously affected by the intermittent pruritus, which was even worse at night. Upon reviewing the patient’s medical history, it was found that the pruritus had started as early as May. It was not mentioned in the chief complaint because it was overlooked. The patient’s first symptom was then clarified as pruritus of the face and lower extremities through the follow-up history.

3. Review And Discussion

3.1. Anti-amphiphysin antibodies and paraneoplastic brainstem encephalitis

The fusion and reuptake of vesicles with the postsynaptic membrane during synaptic transmission is called synaptic vesicle endocytosis (SVE). Amphiphysin is involved in SVE by promoting the division of lattice-protein encapsulated vesicles, which leads to partial failure of message transmission when it is attacked by antibodies (3) (4). In 1993, De Camilli first reported three cases of female breast cancer patients with paraneoplastic stiff person syndrome (SPS). Their anti-amphiphysin antibodies are detected in sera (5). In addition to SPS, patients with anti-amphiphysin antibodies have been found to present with various neurological syndromes, such as encephalomyelitis, myoclonus, and cerebellar syndrome (6) (7). Among these, brainstem encephalitis is an atypical manifestation of encephalomyelitis. As a result, patients often miss the best time for treatment. Ray described a case of anti-Amphiphysin antibody-associated brainstem encephalitis with dizziness and hearing loss as the first symptoms. Her early treatment was delayed due to the visit to an otolaryngologist (8). To our knowledge, such patients with pruritus and dysphagia as the first symptoms have not been reported.

Anti-Amphiphysin antibodies are a relatively uncommon autoantibody. Among 120,000 patients tested over 15 years for paraneoplastic autoantibodies, only 0.06% were positive for anti-Amphiphysin antibodies (7). They occur even more rarely in patients with small cell lung cancer (SCLC), regardless of
the combination of PNS(9). A team performed a count of 116 SCLC patients with the paraneoplastic syndrome but failed to find any with anti-Amphiphysin antibodies (10).

3.2. Pruritus, herpes zoster, and PNS

3 months prior to diagnosis, this patient had suffered from intractable pruritus. However, no such appropriate attention as the first symptom was drawn on and it was even misdiagnosed as an anxiety disorder. It suggests that when there is a patient with chronic pruritus lasting more than 6 weeks, it is essential to consider whether it is an atypical manifestation of the paraneoplastic syndrome (11). The symptom is called "paraneoplastic pruritus" and may be the earliest sign of an underlying malignancy (12). Generally, paraneoplastic pruritus is caused by the lymphatic system, which occurs rarely in solid tumors (13). Insulinoma and colon cancer have both been reported to cause paraneoplastic pruritus(14) (15), suggesting that paraneoplastic pruritus and neuroendocrine tumors are closely connected. Furthermore, SCLC with paraneoplastic pruritus symptoms associated with anti-Hu antibodies was reported(11). While anti-amphiphysin antibodies have rarely been linked to paraneoplastic pruritus in SCLC patients. The case most similar to ours was presented by Berger: A patient with prostate cancer developed intense pruritus on the left side of the face and trunk early in the course of the disease and was ultimately diagnosed with paraneoplastic brainstem disease (16). However, her paraneoplastic antibodies and primary tumor type differ from our patient's.

Two major signaling pathways are known to produce pruritus: 1. the H1 receptor-mediated histamine pathway. 2. the cowhage-stimulated pathway. The cowhage-stimulated pathway primarily involves multi-peaked C-fibers located in the dermis. In layer I of the dorsal horn, the pruritic pathway forms a whole system mediated by inhibitory interneurons with the pain pathway. These interneurons may be the cellular basis for inhibiting pruritus by painful stimuli(17). Meanwhile, anti-amphiphysin antibodies are able to deactivate gabaergic interneurons by reducing the expression of the Na+/K+/2Cl2-cotransporter(18). Thus, it is speculated that it may be one of the mechanisms through which anti-amphiphysin antibodies cause paraneoplastic pruritus by confusing painful sensations with pruritus, which might be further confirmed by primary research. Additionally, tumor tissue secretes excessive interleukin-31 (12) and 5-hydroxytryptamine (5-HT) (15). Paraneoplastic pruritus can also result from them.

Apparently, the most effective measure to control pruritus is to treat the underlying malignancy(12). In addition, molecularly speaking, a block can be made in the second signaling pathway. Gabapentin is the most extensively studied antiepileptic drug to control chronic pruritus (17). It is a structural analog of γ-aminobutyric acid and is thought to increase GABA concentration by affecting its metabolism (19) and block the alpha2delta subunit of voltage-dependent calcium channels in dorsal horn postsynaptic cells(17). Antidepressive agents have also been shown to be applied to paraneoplastic pruritus by affecting serotonin and histamine levels (20). Despite not being widely used, they have shown significant efficacy. (21). Paxitine 20 mg/d is one of the more clinically proven treatments for pruritus, resulting in complete or near-complete relief (20).
Paroxetine 20 mg 1/day and chemotherapy relieved the patient's psychiatric symptoms and pruritus. The effect was observed for 7 days. Although no significant change in facial itching was seen, the pruritus of the lower extremities was significantly reduced.

Our patient had a clinical diagnosis of herpes zoster, which is rare in paraneoplastic dermatoses. Laine reported a case of herpes simplex virus (HSV) infection that was secondary to Castleman syndrome with paraneoplastic pemphigus, and they hypothesized that the erosion of paraneoplastic pemphigus may have increased the body's primary susceptibility to HSV infection or reactivated the latent HSV in the body(22). Paraneoplastic pemphigus is a mucosal skin disease, similar to the paraneoplastic syndrome, which is also triggered by autoimmune processes. However, no case of paraneoplastic syndrome coupled with herpes simplex virus infection has ever been reported. Whether the two are incidental or causative remains to be further investigated.

3.3. Dysphagia and PNS

The patient had progressive dysphagia, while two cranial enhancement MRIs showed no abnormality, and no esophageal neoplasm was seen on the endoscope. On the basis of clinical symptoms and physical examination, brainstem encephalitis was diagnosed. It is believed that antibodies may attack the patient’s swallowing reflex on the central pattern generator (CPG) and the motor component of the swallowing reflex located in the brainstem. With antitumor treatment, the patient's swallowing function improved significantly, confirming that the symptoms were an atypical manifestation of paraneoplastic syndrome.

3.4. Anxiety, cognitive dysfunction, and anti-amphiphysin antibodies

Besides pruritus and dysphagia, the patient also had mild anxiety symptoms, so he was initially given anti-anxiety treatment. Special mention is deserved on the excellent work of Geis. He demonstrated that autoantibodies to amphiphysin inhibit gabaergic neurons by reducing the expression of the Na+/K+/2Cl2-cotransporter(18). On this basis, he found that intrathecal injections of amphiphysin G antibodies purified from one patient induced anxiety behavior in rats (23). It was confirmed that anti-amphiphysin antibodies could cause anxiety in both the macrocosm and microcosm. However, this symptom tends to be more pronounced in SPS. Our patient had no other evidence of trunk and extremity stiffness or typical electromyographic manifestations that could support the diagnosis of SPS. Referring to the relevant diagnostic criteria (24), this patient was not classified as SPS, nor was he ruled out from being in the early stages.

As our patient awaited a definitive diagnosis, he behaved unresponsiveness, which were not resolved with nutritional support. It is assumed that this symptom is related to amphiphysin: Basic studies have shown that mice deficient in amphiphysin will suffer from deficits in learning and memory(25). Decreased levels of amphiphysin 1 mRNA in the hippocampal region in response to repetitive stress may contribute to learning and memory deficits in the elderly (26). In addition, abnormalities in amphiphysin have been
observed in neurodegenerative diseases such as ischemic/hypoxic encephalopathy, epilepsy, stroke, trauma, and Alzheimer's disease (3). More basic researches are expected to demonstrate the relationship between amphiphysin and cognitive dysfunction.

Anxiety disorders and cognitive dysfunction were previously thought to be idiopathic or degenerative. Through our discussion above, it was found that the effects of autoantigens on synaptic transmission and peripheral nerve excitability also appeared to play a crucial role in the diseases' pathogenesis(2). The possibility that central nervous system (CNS) autoimmune antibodies may contribute to idiopathic and degenerative disorders breaks our thinking set.

In this case, the patient suffered from atypical symptoms of paraneoplastic syndrome at an early stage. What he showed was a combination of both brainstem encephalitis and SPS with herpes zoster virus infection. Timely diagnosis and treatment would have a big influence on his quality of life and survival. It prompted us to reevaluate the possibility of the clinical presentation of paraneoplastic syndrome patients with anti-amphiphysin antibodies and the function of the protein named amphiphysin. In conclusion, it is recognized that symptoms such as pruritus and dysphagia do not entirely reflect anxiety states or esophageal cancer. Further screening for the possibility of paraneoplastic syndrome, especially SCLC and anti-amphiphysin antibodies, is absolutely needed.

Declarations

Ethical approval and consent to participate

The study was approved by the Institutional Ethical Committee of the Fourth Hospital of Hebei Medical University and the patient gave written informed consent prior to obtain the data.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the fact that they are in Chinese instead of English, but are available from the corresponding author on reasonable request.

Consent to publish

Written informed consent was obtained from the patient after treatment for publication of this case report. A copy of the written consent is available for review by the Editor of this journal.

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Conflict of interest
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**Author contribution**

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All authors read and approved the final manuscript.

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**References**


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