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Anti-Hu with Paraneoplastic Encephalomyelitis and Small-Cell Lung Cancer: A Case and Review

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Abstract

Paraneoplastic neurological syndromes (PNS) are rare disorders caused by an immune response against neuronal antigens expressed by an underlying malignancy. Anti-Hu-associated paraneoplastic encephalomyelitis (PEM) is one of the most recognized forms, often linked to small-cell lung cancer (SCLC). We report a case of a patient presenting with rapidly progressive cognitive decline, seizures, and peripheral neuropathy. Extensive investigations revealed positive anti-Hu antibodies, suggesting a paraneoplastic etiology. Imaging studies showed limbic system involvement, and a thorough oncological workup confirmed an underlying SCLC. Despite tumor-directed therapy and immunomodulatory treatment, the patient exhibited only partial neurological improvement. This case highlights the challenges in diagnosing anti-Hu-associated PNS due to its heterogeneous presentation and the frequent delay in identifying the underlying malignancy. Early detection and prompt treatment are crucial, as neurological symptoms often precede tumor diagnosis. We discuss the pathophysiology, diagnostic approach, and current treatment strategies, emphasizing the importance of a multidisciplinary approach in managing PNS. This case underscores the necessity for heightened clinical suspicion and early antibody testing in patients with unexplained neurological syndromes, particularly in those at risk for malignancy.

Keywords

Paraneoplastic Neurological Syndrome, Anti-Hu Antibodies, Paraneoplastic Encephalomyelitis, Small-Cell Lung Cancer, Limbic Encephalitis, Peripheral Neuropathy, Autoimmune Neurology, Onconeural Antibodies, Seizures, Neuroimmunology

1. Case Report

We present a 78-year-old male, ex-truck driver, who was admitted to the neuro-

surgery unit, in a Southwest Sydney hospital, with 2 months of bilateral lower limb parasthaesia and weakness. His medical background is only significant for a cholecystectomy, and he was on no medications. He had a smoking history of 50 pack years, although he gave up smoking 10 years ago. He first presented to his General Practitioner two months ago with alternating hot and cold sensations in his thighs. The sensation progressed to his lower extremities with subsequent involvement of distal limbs. He also began to develop numbness in his hands and wrists bilaterally.

Over the next month, he had lost sensation to all modalities. Outpatient CT of thoracic and lumbar spine was normal for his age. Two weeks prior to his admission, he developed pain in his lower back, weakness in his proximal lower limbs bilaterally, and was having difficulty standing from a seated position. He developed urinary incontinence and was constipated. He presented to the hospital following a 2-week history of progressive weakness of proximal lower limbs and lower back pain, with urinary incontinence.

On the initial examination, he was orientated to time and person and had fluent speech. His cranial nerve examination was unremarkable; he had no visual field defect, no diplopia, and a full range of extra ocular movement. His upper limbs showed normal tone, power, reflexes, and sensation to light touch, vibration and pin-prick. His lower limb was significant for proximal weakness in hip flexion and extension (Medical Research Council (MRC) score of 4+/5), absent ankle reflexes, and downgoing plantar reflexes bilaterally. His per rectal exam showed normal sensation, normal anal tone, but no anal wink.

Neurology was consulted for review and management. Magnetic resonance imaging (MRI) scan of the full spine was arranged. It showed no spinal cord compression and only cervical spondylosis at C5 - C6. The only other note was possible consolidation in his right lung base.

General laboratory tests showed no significant findings. His HbA1c, iron, and vitamins b1, b6, B12 and folate were normal. His CRP was elevated to 5.6, and his myeloma screen was negative. Autoimmune screen for dsDNA, rheumatoid factor, ANA and complement was in normal range. A lumbar puncture showed a WCC of 17×10^6 (100% mononuclear), and a significantly elevated protein of 2.58 g and glucose of 4. A paraneoplastic and limbic encephalitis panel was sent.

He subsequently developed significant changes in his neurology in the next 3 days. He developed areflexia in his upper limbs, and lost cold and vibration touch to the level of his sternum. Power in his upper limb was preserved. In his lower limb, his hip power was reduced to MRC 3+/5, and he was areflexic in his knee and ankle. Light touch and vibration were reduced to the level of T10.

A CT chest, abdomen, and pelvis were performed to exclude a paraneoplastic process. It found an enlarged right hilar and precranial lymph nodes, and a 14 mm round lesion in the right kidney. A follow-up PET showed active bilateral hilar and mediastinal lymphadenopathy. A bronchoscopy and biopsy via endobronchial ultrasound confirmed small-cell carcinoma. He was commenced on IVIG for 3 days.

During this time, his serum panel confirmed strongly positive anti-Hu antibodies on indirect immunofluorescence, confirming the diagnosis of paraneoplastic neuropathy. His autoimmune panel was otherwise negative for other common antibodies, including amphiphysin, Hu, Ri, YO, Ma/Ta, CRMP5, SOX-1, Titin, Zic and GAD65. His limbic encephalitis panel was also negative. Nerve conduction studies of upper and lower limbs showed a severe generalized sensory peripheral neuropathy affecting the radial nerve bilaterally, sural and tibial nerve bilaterally.

Unfortunately, despite IVIG, his condition worsened and he developed severe confusion, visual hallucinations and focal onset seizures with altered awareness. A repeat LP and MRI were performed to exclude an infective process and investigate for limbic encephalitis. His LP showed a WCC of 40 (mononuclear), without organisms on gram stain. CSF protein levels remained elevated at 2.46 g and CSF glucose of 4. His meningitis panel, including HSV, was negative. An MRI with Gadolinium showed hyperintensity in bilateral medial temporal lobes, consistent with limbic encephalitis (Figure 1). He was commenced on Keppra 1000 mg twice daily for his seizures, and pulsed methylrprednisone 1000 mg IV daily for 2 days, followed by 60 mg prednisolone daily. He was given sulfamethoxazole-trimethoprim for PJP cover. His seizures ceased, but despite methylprednisone, he showed little cognitive improvement. He was given a further 3 days of IVIG (2 g/kg total dose), in addition to ongoing prednisolone. Since then, he has made significant clinical improvement in his cognition. He was alert, orientated to time person and place, and answered questions appropriately. He could follow simple commands.

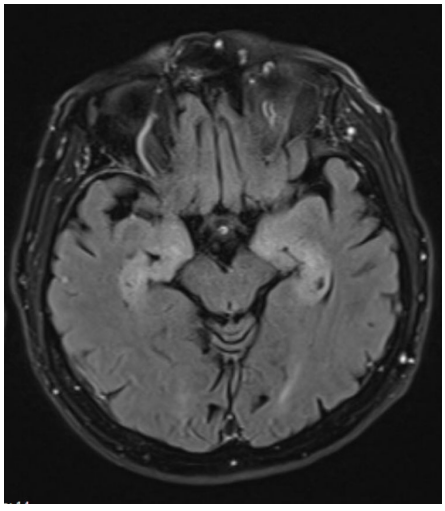

Figure 1. FLAIR sequence. Hyperintensities in the subcortical white matter, involving the medial temporal lobes bilaterally.

He was reviewed by the medical oncology team, and on basis of his premorbid function, preserved renal and liver function, he was offered a trial of systemic chemotherapy. His neurological deficits of lower limb weakness, sensory changes, and areflexia persisted. He died 3 months later, secondary to his malignancy.

2. Discussion

The Hu protein family consists of 4 members: HuA, HuB, HuC, and HuD. Whilst HuA is ubiquitous, HuB, HuC, and HuD are restricted to neurons [1]. HuD is also expressed by SCLC cells, suggesting the development of an immune response that cross-reacts with neuronal Hu proteins [2]. However, the pathological role of anit-Hu antibodies in neurons and the development of paraneoplastic neuropathy and paraneoplastic limbic encephalitis are unclear. Although *in-vitro* studies showed that anti-Hu IgG preparations could kill human expressing HuD cell lines [3], the administration of anti-HuD IgG did not result in CNS lesions in mice [4].

The association between anti-Hu antibodies and paraneoplastic syndromes, particularly from small-cell lung cancer, is well known. Although previously believed to be a rare phenomenon, recent studies have developed our understanding. Detection of a paraneoplastic encephalopathy should prompt investigation towards finding an underlying malignant small-cell lung cancer. An observational study in France detailed 632 patients with definite PNS or autoimmune encephalitis, showing that small-cell lung cancer was the most common in relation to PNS, with a median age of 62.1. The most common antibodies were anti-NMDA, anti-LG1 and anti-Hu (in that order) [5]. Although the prevalence of AE and PNS in this study was 3.6 and 4.1/million respectively, these slightly differed from other regions, where rates of 5 - 9/million were observed [6].

The clinical manifestations of anti-Hu paraneoplastic syndrome are varied. Clinically, they present as manifestations of the anatomical sites involved. The median time between development of neurologic symptoms and tumour diagnosis in one study was 4 months [2]. A majority of patients may have manifestations of neurologic disease prior to diagnosis of tumour. When there is widespread neural dysfunction, involving two or more regions, such as temporal lobes, limbic area, and dorsal root ganglia, it is termed paraneoplastic encephalomyelitis (PNE) [7]. In a study of 200 patients with anti-Hu, the predominant feature was sensory neuropathy (54% of patients). Sensorimotor neuropathy and dysautonomia were the least commonly found features [8]. Paraneoplastic limbic encephalitis is another manifestation of the syndrome and is characterised by subacute cognitive dysfunction with severe memory impairment, seizures and psychiatric features. The diagnosis requires 4 key clinical criteria: clinical picture of seizures, memory loss, confusion or psychiatric symptoms suggesting temporal lobe involvement; temporal relationship of less than 4 year between neurological symptoms and cancer diagnosis; absence of metastatic disease, metabolic encephalopathy, sepsis, drug-related or other cause that could account for the neurological dysfunction; abnormal MRI of the hear characterised by high intensity T2 weighted images and atrophy on T1 weighted images in one or both medial temporal lobes [9].

Serum anti-Hu-antibodies are highly specific for paraneoplastic syndromes (99%) with a sensitivity of 82% [10]. False positives can occur in other diseases, such as Sjögren, and should be studied with both immunohistochemistry and western blot analysis to reduce the error rate. In patients with small-cell cancer that is not initially

detected with CT chest and bronchoscopy, serial screening should be performed, given the highly correlated association.

MRI findings of the most typical paraneoplastic limbic encephalitis are bilateral mesial temporal signal abnormalities, without notable gadolinium enhancement [11]. EEGs are also useful in the diagnosis of paraneoplastic limbic encephalitis. A single-centre retrospective study found that EEG was the most sensitive investigation, with generalised or focal slowing as the most commonly observed abnormalities [12].

The treatments of PNE can involve the treatment of the underlying tumour and immunosuppressive therapy. The corner-stone of managing PNL however is treating the underlying malignancy. In a case study of 200 patients, regardless of the use of immunotherapy, an improvement and stabilization of PNL occurred, with a 4.5× greater odds ratio [8]. However, treatment of the tumour can not be the only approach to management, despite the beneficial effect. Some studies indicate that paraneoplastic encephalitis may still progress even when complete response of the tumour is achieved [13]. Immunosuppressive agents that have been used in anti-Hu PNL include corticosteroids, intravenous immunoglobulin (IVIG), cyclophosphamide and/or plasmapheresis. Studies have consistently shown that those with high Rankin scores (>3) were often associated with poorer response to therapy [8]. Furthermore, those with lower Rankin scores were more likely to achieve disease stability, but not necessarily complete remission [13]. Mortality from disease is rarely from tumour, but rather the complications of encephalopathy, including respiratory failure, from neuromuscular weakness or brain-stem damage, and cardiac arrhythmia from autonomic dysfunction. Interestingly, patients with anti-Hu paraneoplastic encephalitis have lower mortality from small-cell lung cancer tumour burden, but overall mortality remains similar [8].

Anti-Hu paraneoplastic syndrome is highly heterogenous, with symptoms resulting in changes to the sensory system (54%), motor system (45%), brain stem (31%), autonomic system (28%), cerebellar symptoms (25%), and limbic systems (22%) [2]. In those presenting with limbic encephalitis, it has been proposed that patients respond poorly to tumour therapy or immune therapy [14]. In a retrospective study that identified 18 patients with anti-Hu limbic encephalitis, only 5/13 showed improved neurological improvement. Treatment of the tumour itself seemed to have more effect on neurological improvement than use of immunosuppressive treatment.

In adults presenting with peripheral polyneuropathies and a history of smoking, paraneoplastic syndrome secondary to lung malignancy should be considered. Anti-Hu is a common marker of paraneoplastic disease, although the mechanisms of these antibodies in relation to the disease are poorly understood. In this syndrome, disease may evolve to cause limbic encephalitis, for which EEG provides a sensitive test, and MRI can identify classic findings in the mesial temporal lobes. Treatment involves the management of the underlying malignancy, and response to additional immunotherapy, especially in late disease, is poor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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