CASE REPORT

A case of confusion: paraneoplastic encephalomyelitis in an elderly patient suspected of having urinary tract infection-associated delirium

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SUMMARY

Acute confusion is a common symptom of physical illness in the older patient. In the majority, it is transient and resolves on treatment of precipitants. In a subset of patients, however, neurological decline is progressive, raising concern about a serious underlying cause.

We describe the case of a 71-year-old woman who developed progressive cognitive impairment following insertion of a permanent pacemaker for sinoatrial arrests. An initial diagnosis of delirium secondary to a urinary tract infection was suspected; however, the patient became increasingly confused despite treatment. Laboratory tests revealed serum anti-Hu paraneoplastic antibodies, and CT chest identified an occult lung tumour. Cervical lymph node histopathology confirmed a diagnosis of small cell carcinoma of the lung. Although a rare cause of confusion, paraneoplastic encephalomyelitis should be recognised early to allow timely identification and treatment of the associated cancer.

BACKGROUND

Paraneoplastic neurological syndromes (PNSs) are rare manifestations of systemic cancer affecting the central or peripheral nervous systems, which do not originate from direct tumour growth or other causes, such as metastatic, metabolic or treatment-related complications of malignancy. PNSs are thought to arise as a result of an antitumour immune response, in which neuronal antigens ectopically expressed by cancer cells trigger the production of autoantibodies.¹ Interactions between these onconeural autoantibodies and physiologically expressed antigens in the central or peripheral nervous system lead to immune-mediated neuronal toxicity and ultimately cell death.² Tumours most commonly associated with PNSs are those expressing neuroendocrine proteins (eg, neuroblastoma and small cell lung cancer (SCLC)), those containing immature neuronal tissue (eg, teratoma) or those involved in immunoregulatory function (eg, thymoma). Due to differences in tumour type and onconeural autoantibody profile, there is significant heterogeneity in the clinical presentation of PNSs. To aid diagnosis, eight classical PNSs have been described, each associated with different tumour and autoantibody profiles (table 1).

One of the most common PNSs is paraneoplastic encephalomyelitis, which is characterised by patchy, multifocal involvement of cerebral cortex,

cerebellum, limbic system, brainstem and spinal cord.³ This diffuse pathology can be explained by the presence of high circulating levels of anti-Hu antibodies that target intraneuronal RNA-binding nuclear proteins.⁴ Anti-Hu paraneoplastic encephalomyelitis is associated with an underlying SCLC in approximately 75%–85% of cases.^{2,4} Interestingly, the neurological syndrome frequently manifests before the identification of the underlying malignant culprit.

Case presentation

A 71-year-old woman presented to the Accident & Emergency Department with a 1-day history of recurrent syncope. ECG revealed an 8 s sinoatrial arrest, prompting insertion of a permanent cardiac pacemaker. In the 2 weeks following the procedure, the patient developed acute confusion, inattention and short-term memory loss. Collateral history from the patient's daughter revealed that the patient had also reported progressive low mood over the past 3 months and had been commenced on citalopram by her general practitioner 1 week previously. On examination, the cardiac and pulmonary systems were unremarkable. Abdominal examination revealed mild suprapubic tenderness. Neurological examination revealed objectively low mood, moderate cognitive impairment and bilateral gaze-evoked horizontal nystagmus.

The patient had a medical history of chronic obstructive pulmonary disease, hypothyroidism and diverticular disease and was a current smoker (40 pack-years). Regular medications included levothyroxine, tiotropium and beclometasone dipropionate/formoterol fumarate inhalers. There was no known family history of medical conditions.

Investigations

Laboratory tests showed a mild neutrophilia ($8.6 \times 10^9/L$) and elevated C reactive protein (8.8 mg/L). Liver and thyroid function tests were normal. Random cortisol, calcium, vitamin B12 and folate levels were also normal. Renal function tests showed a low serum sodium level (122 mmol/L) but were otherwise unremarkable. Urinary osmolality was inappropriately elevated (544 mOsmol/kg) relative to serum osmolality (258 mOsmol/kg), and urinary sodium levels were high (62 mmol/L), confirming a diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Urine culture revealed $>10^5$ cfu *Escherichia coli*.

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Table 1 Classical paraneoplastic neurological syndromes, their associated tumour origin and autoantibody profile^{1,2}

Clinical syndrome	Associated tumours	Autoantibodies
Subacute cerebellar degeneration	SCLC, breast, ovarian, Hodgkin's disease	Anti-Yo/Hu/Tr/CV2/VGCC/Ri
Limbic encephalitis	SCLC, testicular, breast, thymoma	Anti-Hu/CV2/Ma2/NMDAr/AMPAr
Paraneoplastic encephalomyelitis	SCLC	Anti-Hu/CV2/amphiphysin
Opsoclonus myoclonus	SCLC, breast, neuroblastoma	Anti-Ri/Hu
Subacute sensory neuropathy	SCLC	Anti-Hu/CV2/amphiphysin
Chronic gastrointestinal pseudo-obstruction	SCLC	Anti-Hu
Lambert–Eaton myasthenic syndrome	SCLC	Anti-VGCC
Dermatomyositis	Ovarian, lung, colorectal, breast	Anti-P155

SCLC, small cell lung cancer.

Chest radiograph showed no evidence of focal consolidation or lymphadenopathy. CT scan of the brain revealed no evidence of stroke or mass lesions. It was not possible to perform MRI due to recent cardiac pacemaker insertion.

The patient's confusion was initially attributed to delirium, precipitated by a urinary tract infection (UTI), recent pacemaker procedure and citalopram-induced SIADH. The patient was treated with a 5-day course of trimethoprim. Citalopram was stopped, and sodium levels gradually improved with fluid restriction (1.5 L/day), reaching a peak of 134 mmol/L at 2 weeks. Despite near normalisation of sodium levels and treatment of the UTI, the patient became progressively more confused. In the third week, hyponatraemia began to worsen despite ongoing fluid restriction, prompting investigation of alternative causes of SIADH. To exclude lung malignancy, a repeat chest radiograph was performed that revealed possible enlargement of the right hilum. CT scan of chest, abdomen and pelvis with contrast identified an 18.5 mm paratracheal mass, mediastinal and subcarinal lymphadenopathy, as well as a suspected metastasis in the right lobe of the liver (figure 1). To obtain tissue for histopathology, a fine needle aspirate (FNA) of a cervical lymph node was performed. Due to the patient's inability to retain information regarding the indication for the FNA, she was deemed to lack mental capacity to consent to the procedure. Following

Figure 1 CT scan in coronal plane demonstrating 18.5 mm right paratracheal mass (arrow), mediastinal and subcarinal lymphadenopathy and a metastasis in right lobe of the liver.

discussion with the patient's daughter, it was decided to proceed with the FNA in the patient's best interests, and a consent form 4 was signed. Despite her confusion, the patient cooperated throughout the FNA, without need for any pharmacological sedation. Histopathology of extracted lymph node tissue revealed small cell carcinoma. To exclude brain metastases as the cause of worsening confusion, repeat CT scan of the head was performed, which showed no evidence of mass lesions. Analysis of antineuronal antibodies present in the serum showed strong positivity for anti-Hu immunoglobulin, compatible with a diagnosis of anti-Hu-associated paraneoplastic encephalomyelitis.

Treatment

At the time of diagnosis, the patient was confined to a bed and unable to perform any self-care activities (Eastern Cooperative Oncology Group performance status grade 4).⁵ Due to poor performance status and advanced cognitive impairment, the patient was not deemed fit for systemic chemotherapy. Treatment focused on palliative symptom control and management of recurrent generalised tonic-clonic seizures with sodium valproate.

Outcome and follow-up

The patient died of respiratory failure secondary to extensive stage SCLC 6 weeks after diagnosis.

DISCUSSION

The causes of acute confusion in the older patient are numerous and diverse. Among the most common is delirium, which can be identified in 8%–17% of elderly patients presenting to the emergency department⁶ and can be attributed to an array of underlying medical conditions or treatment complications.⁷ In the present case, an initial diagnosis of delirium was suggested by acute onset of cognitive decline and inattention, in the context of multiple medical problems (ie, UTI, pacemaker procedure and moderate hyponatraemia) and predisposing risk factors (eg, older age and depression).

Suspicion of an alternative diagnosis was raised as the patient became more confused, despite the treatment of UTI and resolving hyponatraemia. Prior to admission, she had a high baseline functional status and still worked in a local charity shop. In the absence of premorbid cognitive impairment or frailty, prolonged delirium was considered unlikely. In addition, although older female patients are considered those most at risk, the majority of SSRI-associated hyponatraemia cases will resolve within 2 weeks of discontinuing the drug.^{8,9} In this case, hyponatraemia persisted despite ongoing fluid restriction and 4 weeks since discontinuation of citalopram. To identify the cause of persistent SIADH, a CT scan of the chest was performed, which revealed a small paratracheal mass and associated lymphadenopathy. Subsequent screening for serum antineuronal antibodies was the critical investigation because a diagnosis of anti-Hu paraneoplastic encephalomyelitis could account for the complete clinical syndrome: depression, cognitive impairment, nystagmus, autonomic dysfunction and generalised seizures. As in the majority of PNSs, neurological symptoms preceded the diagnosis of a specific cancer.² It is not uncommon for the underlying tumour to be sufficiently small in size as to avoid detection by conventional imaging methods, including high-resolution CT scanning.^{10,11} In patients with circulating paraneoplastic antibodies and no identifiable primary tumour, a whole-body positron emission tomography with fluorodeoxyglucose would be indicated.²

As immune-mediated neurological syndromes, the main treatments for PNSs are to reduce antigen production by antitumour therapy and to suppress the immune response by removing antibodies from the serum (eg, intravenous immunoglobulin, and plasma exchange). Depleting paraneoplastic antibodies is considered beneficial when cytotoxicity is mediated by antibodies targeted against cell surface/synaptic proteins (eg, anti-VGCC and anti-NMDAR).² In contrast, disorders with antibodies directed against intracellular antigens, such as anti-Hu encephalomyelitis, are less likely to respond to antibody removal therapies, as the underlying pathogenic mechanism is thought to be T-cell mediated.² Although these disorders occasionally show transient stabilisation with immunosuppressants such as cyclophosphamide, it is not possible to reverse existing neuronal loss.^{2,3,12,13} Overall, less than 10% of patients with anti-Hu paraneoplastic encephalomyelitis show neurological improvement after aggressive antitumour treatments and immunotherapy.³ The rare responders are typically those with limited neurological deficits on initiation of treatment. Thus, although symptoms of PNSs are often non-specific, early diagnosis is critical to allow treatment before the onset of severe neurological disability. In

a patient with progressive neurological decline, smoking history and SIADH, a PNS secondary to lung cancer should be excluded at an early stage, even in the presence of normal chest imaging.

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Learning points

- Paraneoplastic neurological syndromes (PNSs) are rare manifestations of systemic cancer characterised by progressive and debilitating neurological symptoms.
- The majority of patients presenting with PNSs do not have a pre-existing cancer diagnosis and a small primary tumour can be missed on imaging.
- Paraneoplastic encephalomyelitis should be considered as a cause of acute confusion in older patients where there is no obvious precipitant, especially in the absence of pre-existing cognitive impairment.
- Early detection of paraneoplastic antibodies in the serum or cerebrospinal fluid reduces morbidity and mortality through early identification and treatment of cancer

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