

Paraneoplastic syndrome presenting as progressive cognitive decline

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Abstract

A number of paraneoplastic neurological syndromes have been described in association with small cell lung carcinoma and, less commonly, with other malignancies. We describe here the case of a 58-year-old woman with paraneoplastic limbic encephalitis (PLE) complicating squamous cell carcinoma of the lung.

She presented with subacute cognitive decline, particularly memory loss, personality change and hallucinations. She had a history of ischaemic heart disease and an undifferentiated connective tissue disorder. Apart from a low titre of anti-nuclear antibody, all blood and CSF tests were normal, including inflammatory markers. CT scans of the brain demonstrated multiple low-density lesions in the cortex and cerebellum, but MRI of the

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brain only demonstrated lesions in the right frontal lobe and the right occipital lobe which did not have the appearance of metastases. Trans-oesophageal echocardiography, carotid doppler ultrasonography and a 24-hour tape all failed to identify any source of embolus. EEG demonstrated bilateral fronto-temporal changes.

Subsequently a suspicious right upper lobe lesion on chest radiography was confirmed on CT, and bronchoscopy revealed a second right lower lobe endobronchial mass; biopsy confirmed squamous cell carcinoma.

Early recognition of paraneoplastic syndromes like PLE should result in prompt diagnosis and treatment of these cancers.

Keywords

Paraneoplastic; encephalitis; squamous cell; lung cancer.

Introduction

Paraneoplastic neurological syndromes (PNS) complicate less than 1% of malignancies and often predate the diagnosis of cancer^[1]. PNS have been described with a number of cancers but occur most commonly in association with small cell lung carcinoma (SCLC)^[2]. We present a case report of paraneoplastic limbic encephalitis (PLE) in association with squamous cell carcinoma of the lung.

Case report

A 58-year-old woman was presented with a one-week history of headache, left-sided visual loss, mild left-sided weakness, slurring of speech, and confusion, with a background of two weeks of increasing confusion and behaving 'unlike herself' according to her family. She had a history of stable ischaemic heart disease and an undifferentiated connective tissue disorder, and had smoked 10 cigarettes a day for 40 years. Her treatment included

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aspirin, glyceryl trinitrate spray and 50 mg azathioprine daily. On examination, she was confused, particularly disorientated in time, and had a left homonymous hemianopia, mild left hemiparesis and an ataxic gait. Initial routine haematological and biochemical tests were normal (Hb 11.3 g/dl, WBC count of $10 \times 10^3/\mu\text{l}$, platelet count of $129 \times 10^3/\mu\text{l}$, INR 1.0, APTT 26 s, ESR 34 mm/h and CRP 3 mg/l). The initial chest radiograph was reported as normal. CT brain (without contrast) revealed a low-density lesion in the left cerebellar hemisphere, presumed to be infarction (Fig. 1(a)).

Over the following 10 days her weakness and ataxia resolved. However, the headaches persisted, a pyrexia of 37.5°C arose, and her cognitive function progressively deteriorated with development of hallucinations. Further personality change was noted, the patient becoming vacant, distractible and occasionally confrontational with a mild dressing dyspraxia and perseveration of movement. Mini mental state examination score was 17/30 with impairment of attention and short-term recall. No focal neurological deficits could be demonstrated. Routine blood tests remained normal and repeat ESR was 15 mm/h. No infection was found and causes of 'treatable' dementia were excluded (red cell folate $188 \mu\text{g/l}$, TSH 2.2 pmol/l and total T3 18.2 pmol/l, and Treponemal serology negative). A borderline low vitamin B₁₂ (139 ng/l) was promptly treated. Anti-nuclear antibody was demonstrated at a titre of 1 in 160, but no extractable nuclear antigen, anticardiolipin, or lupus anticoagulant antibodies were present and serum complement levels were normal (C3 1.19, C4 0.28). Cerebrospinal fluid had mildly elevated protein (465 mg/l) but white and red cell counts ($1/\text{mm}^3$ and $25/\text{mm}^3$ respectively) and glucose (2.9 mmol/l compared to a plasma glucose of 5.3 mmol/l) were within normal limits. There was no growth on culture of CSF, no herpes simplex virus 1 or 2 detected by PCR, and no antibodies to Epstein Barr virus or cytomegalovirus present. Repeat CT brain (without contrast) nine days later showed new lesions in the right posterior frontal, right cerebellar and right occipital regions and persistence of the left cerebellar hypodensity (Fig. 1(b, c)).

The impression was of diffuse cerebrovascular disease causing progressive cognitive decline in view of risk factors for arterial disease and CT brain appearance. However, no embolic cause of cerebral infarcts was found; trans-oesophageal echocardiography, carotid doppler ultrasonography and a 24-hour tape were normal.

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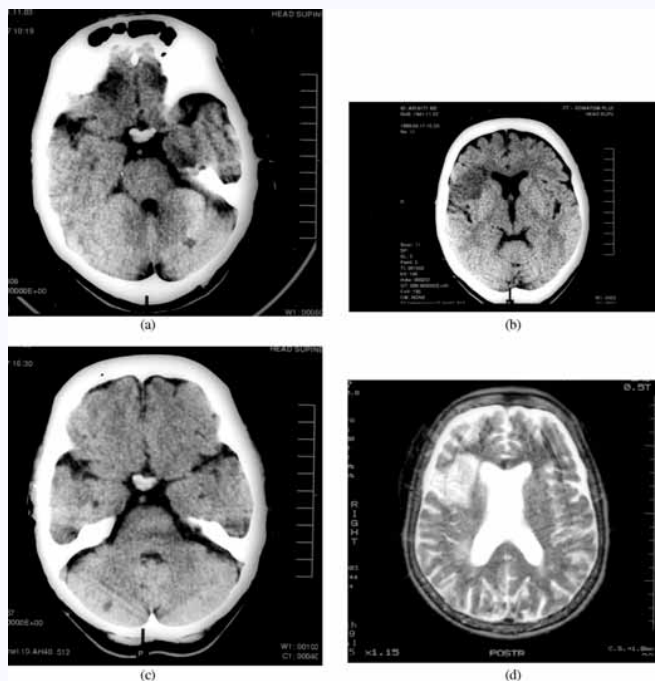


Fig. 1. (a) CT brain (without contrast) on Day 1 showing a low-density lesion in the left cerebellar hemisphere. (b) CT brain (without contrast) on Day 10 showing a new low-density lesion in the right posterior frontal region. (c) CT brain (without contrast) on Day 10 showing a new low-density lesion in the right occipital region. (d) MRI brain (without gadolinium enhancement) on Day 26 showing a lesion in the right posterior frontal region.

A repeat plain chest radiograph suggested an ill-defined 1-2 cm opacity in the right upper lobe suggestive of malignancy. CT scans of the chest and abdomen showed discrete masses in the right upper lobe of the lung (4 cm in diameter) and the right

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Fig. 2. CT chest showing 4 cm right upper lobe mass.

kidney (3 cm in diameter) in association with mediastinal lymphadenopathy (Fig. 2). Fibre-optic bronchoscopy detected a small right lower lobe endobronchial mass and biopsies confirmed squamous cell carcinoma.

In this context, the clinical presentation was compatible with a PLE, multiple cerebral metastases or CNS vasculitis. Active vasculitis was felt to be unlikely given the low levels of inflammatory markers. MRI of the brain (without gadolinium enhancement as the patient became agitated) failed to show multiple cerebral lesions as on the CT; two areas of increased signal density were seen in the right frontal lobe and right occipital lobe (Fig. 1(d)). An EEG showed prominent bilateral fronto-temporal slow activity, more marked on the right.

The patient declined rapidly and died before chemotherapy was commenced. No autopsy was performed at the family's request. The final diagnosis was squamous cell carcinoma of the lung complicated by a PLE, based on the clinical picture of progressive insidious cognitive decline and multiple discrete cognitive defects, involvement of the temporal

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lobes on EEG, exclusion of causes of dementia, embolic cerebral infarcts and multiple metastases, and co-existence of cancer.

Discussion

PNS are due to non-metastatic remote effects of a cancer on the nervous system. Different syndromes are described; most have been found in association with small cell carcinoma of the lung, particularly Lambert-Eaton syndrome and encephalomyelitis. PNS are thought to relate to cross-reactivity of antibodies against tumour cell antigens with neuronal cell antigens but this is unconfirmed. Specific anti-neuronal antibodies can be demonstrated in a proportion of cases. In the largest study of PLE and SCLC that involved 16 patients, 50% of these patients had anti-Hu antibodies^[3]. Patients with PLE and tumours other than SCLC usually have no identifiable anti-neuronal antibodies^[4]. Therefore, absence of these antibodies does not exclude the diagnosis of PLE and no cause-effect relationship between the antibodies and PLE has been demonstrated^[3,4].

PLE is the condition of inflammation of the limbic areas of the cerebral cortex occurring in association with cancer. It was first described by Brierley, Corsellis, Hierons and Nevin in 1960^[5]. PLE is most commonly associated with SCLC but there are also case reports in association with malignancies of breast, ovaries, germ cells, colon and bladder, Hodgkin's lymphoma, and thymoma^[2,6,7]. To our knowledge only three cases have been described in association with a non-small cell lung carcinoma (NSCLC)^[8]. Classically it presents with subacute confusion, amnesia and psychiatric symptoms. Seizures may also occur^[2,9]. Temporal lobe abnormalities are usually apparent on MRI or EEG. Brain MRI can have abnormal signal in the temporal lobes on T2-weighted images or can be normal^[10,11]. Elevated protein, mild lymphocytic pleiocytosis, elevated Ig G and oligoclonal bands may be present in the CSF, but at least 10% have normal CSF^[1,3]. EEG irregularities occur in approximately 75% of patients, the classical picture being focal bi-temporal slow activity or paroxysmal sharp waves and spikes^[4]. At post-mortem the most consistent abnormalities are neuronal loss, gliosis and microglial nodules in the hippocampus and amygdala^[5,7].

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PLE in association with NSCLC is not well documented so little is known about the course of the neurological symptoms and response to treatment. However, more is known in SCLC. The course of PLE complicating SCLC is variable and may be related to the presence or absence of anti-Hu antibodies. In the 16-patient study of PLE and SCLC, patients who were anti-Hu antibody positive tended to develop a multifocal neurological disorder compatible with paraneoplastic encephalomyelitis (in which all areas of cerebral cortex, cerebellum, brainstem, spinal cord and peripheral nervous system can be involved) rather than isolated PLE^[3]. These patients' neurological symptoms were less responsive to treatment of the primary tumour or immunosuppressive agents such as steroids, and they tended to die of the neurological disorder rather than progression of the cancer. Conversely, patients with no anti-Hu antibodies were more likely to present with PLE alone, which was more amenable to anti-neoplastic and immunosuppressive treatment, and they tended to die from cancer progression^[1]. Patients with thymoma or Hodgkin's disease and PLE appear to have a good chance of significant neurological improvement with anti-tumour treatment or immunosuppressants^[7]. Rarely patients show spontaneous neurological improvement independent of their tumour status or can present with PLE after apparent cure of a previously diagnosed tumour^[9].

PNS such as PLE are important for both practical and academic reasons. Firstly, in over half the patients neurological symptoms precede the diagnosis of cancer, in some cases by up to 5 years, but the median duration of symptoms in those presenting with PLE is 3.5 months^[8]. Thus, the recognition of PNS should initiate a search for malignancy and hopefully result in earlier diagnosis and treatment. Secondly, PNS are source material for research into immunological mechanisms involved in cancer, which may be fruitful in devising new therapies for PNS and cancer itself.

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