

Case Report

# Paraneoplastic limbic encephalitis in an elderly patient with small cell lung carcinoma

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## ABSTRACT

We report a case of paraneoplastic limbic encephalitis (PLE) in an elderly lady with small-cell lung carcinoma (SCLC) and positive anti-RI neuronal auto-antibody. PLE is a relatively rare clinical entity associated with cancer patients, but is probably under-diagnosed. PLE typically presents clinically with affective changes in personality, cognitive dysfunction and seizures in a patient with malignancy, particularly SCLC. Although diagnosis does not rely upon definitive investigation results, serum paraneoplastic antibodies, abnormal CSF, and characteristic MRI and EEG findings may support the diagnosis. As PLE often presents prior to the discovery of a primary tumour, knowledge of the disease may assist in identifying underlying malignancy.

## INTRODUCTION

Paraneoplastic syndromes are a common complication of many malignancies, occurring in up to 50% of cancer patients. They involve a wide spectrum of disease processes, causing symptoms not due to direct invasion of the primary tumour or metastases. Neurological paraneoplastic syndromes cause remote effects by an immune-mediated response against normal neuronal tissue. Paraneoplastic limbic encephalitis (PLE) affects a small, but probably underestimated, proportion of all cancer patients. PLE most commonly affects patients with squamous cell carcinoma of lung (SCLC), though it has also been reported in breast, testicular, and thymus cancers, transitional cell carcinoma of the bladder, and Hodgkin's lymphoma. There has been no age, race, or sex preference reported in the literature.

The limbic system incorporates the hippocampus, hypothalamus, thalamus, amygdala, fornix, and other structures surrounding the brainstem and plays a central role in memory, learning, and higher emotion. Antigens expressed by the tumour produce antibodies, which cause an immune-mediated response against the healthy nervous system, and thus the term paraneoplastic limbic encephalitis implies inflammation within the limbic system as a result of a paraneoplastic process.

We report a case of PLE associated with SCLC. Our primary aim is to heighten awareness of the disease entity to assist prompt initiation of appropriate investigations and improved levels of diagnosis.

## CASE REPORT

An 85-year-old ex-smoker (50 pack years) presented with increasing shortness of breath and was diagnosed histologically with small-cell lung cancer. PET/CT scans at time of diagnosis confirmed a very large left hilar tumour, with extensive mediastinal involvement, but no distant metastases were identified. Prior to this she had been in good health, with no significant past medical or family history. The patient underwent 4 cycles of chemotherapy with carboplatin and etoposide the following month. She subsequently received adjuvant radiotherapy, with 15 treatments to the chest and 12 treatments to the brain. The cranial irradiation she received was a prophylactic measure, as SCLC has a predilection for CNS spread. Subsequent CT scanning confirmed a positive response to treatment, with a significant reduction in the size of the tumour and nodes.

The patient remained at home during her treatment, maintaining a reasonably good functional status. Her usual positive and outgoing personality prevailed throughout this period, although family members noticed a gradual impairment of her memory within two months of completion of her treatment. A more acute deterioration occurred six months post-diagnosis, when the patient collapsed at home. There was incontinence of faeces and urine, succeeded by marked confusion. A diagnosis of seizure was considered likely, but could not be confirmed as the episode was unwitnessed. The patient was admitted to an acute medical unit and a mini-mental score examination was recorded as 2/10. There was no focal neurology elicited. A full septic screen was negative. Routine serological tests were normal. A CT of her brain again demonstrated no evidence of cerebral metastatic disease, and a further CT of her chest showed the tumour and mediastinal nodes to be smaller than two months previously.

There followed a state of fluctuating confusion, which persisted with impairment of both short and long term memory. The most notable feature reported by the patient's family was a marked change in personality. She had previously had a positive and outgoing personality, which had remained

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even throughout her cancer treatment. However, following her collapse and subsequent admission the patient was found to be apathetic, uninterested in her family, and unsettled, with episodic agitation. This caused great distress to those close to the patient. The patient fell in hospital and unfortunately sustained a fractured left neck of femur. MMSE at this time was 4/10, and a further CT brain showed generalised atrophic change, again with no evidence of metastatic spread. The patient successfully underwent surgical fixation of her hip fracture, but progress with rehabilitation was poor primarily due to her poor cognitive state.

A diagnosis of paraneoplastic limbic encephalitis was considered on admission, and appropriate investigations were initiated. Serum paraneoplastic antibodies subsequently returned as positive for anti-RI antibodies, a highly specific paraneoplastic neuronal antibody. CSF was not obtained, as lumbar puncture was not felt appropriate given the patient's condition. Electroencephalogram showed background activity within normal limits, but with frequent generalised slowed activity throughout the recording. Some sharp wave activity was seen in the left mid-temporal region, representing a mild encephalopathy. Cranial MRI was performed but unfortunately the study was of poor quality due to patient movement, enabling only generalised cortical atrophy to be identified.

The clinical presentation with confusion, memory loss, change in personality and probable seizure in a patient with SCLC were consistent with a diagnosis of PLE. Both the EEG findings and anti-RI antibodies supported the diagnosis. Symptomatic management was deemed the most appropriate approach, and the patient died three months after her presentation of collapse. A post mortem was not performed.

## DISCUSSION

The first report of a mental disorder associated with primary lung carcinoma was described in 1956<sup>1</sup>. Corsellis subsequently coined the term 'Limbic Encephalitis' in 1968, detailing the association with carcinoma<sup>2</sup>. Sporadic case reports followed, with only 16 cases verified clinically by 1990. The past decade has witnessed increasing interest in the condition. Improved recognition has allowed for structured data collection and small studies to take place. An inherent difficulty surrounds enrolment to these studies in that patients are frequently very unwell when the disease process is recognised. The condition is characterised by cognitive impairment, confusion, memory loss (usually short term), personality change, and seizures (usually complex-partial, but may be generalised). Olfactory and gustatory hallucinations are less commonly reported. There is usually a sub-acute presentation of symptoms over weeks or months. Symptoms may precede the diagnosis of underlying malignancy in up to 60% of cases<sup>3</sup>. It is therefore important to consider the diagnosis in any patient with unexplained cognitive changes, and not only those with a known diagnosis of cancer.

In this case report the presence of SCLC, coupled with a classical history of cognitive dysfunction, personality change, and possible seizure activity was strongly suggestive of PLE. The subsequent detection of a highly specific paraneoplastic antibody in the patient's blood supported the diagnosis. Autoimmune antibodies may serve as a helpful

diagnostic tool, but their exact role in causing neuronal injury and clinical manifestations remains unclear. Neuronal autoantibodies tested for routinely are anti-HU (ANNA-1), anti-RI (ANNA-2), and anti-YO (PCA-1). Of these, anti-HU is the most commonly found, occurring in approximately 50% of cases of PLE<sup>4</sup>. The anti-RI antibodies discovered in our patient are less commonly found, but are the most specific for supporting a diagnosis of PLE. Voltage-gated calcium channel antibodies are also tested for as part of the paraneoplastic antibody assay. These were negative in this particular case. The prevalence of these markers in patients who definitely do not have a neuronal paraneoplastic syndrome is not reported. CSF may show mild elevation of proteins, paraneoplastic antibodies, pleocytosis, and positive oligoclonal bands, or intrathecal IgG. Unfortunately a CSF sample was not obtained in the patient discussed. EEG may be normal, but as in this case often displays non-specific generalised or focal slowed activity, which may depend on the stage of the disease. Characteristic MRI findings in patients with PLE include unilateral or bilateral medial temporal signal abnormalities, which are best identified on T2-weighted images. These are not found in every patient with PLE, but are reported in between 57%<sup>3</sup> and 83%<sup>5</sup> of cases.

This latter retrospective review<sup>5</sup> studied twenty-four patients attending the Mayo Clinic with suspected PLE on the basis of classical symptoms and the presence of cancer. Thirteen of these patients had a diagnosis of SCLC. The common clinical findings were cognitive dysfunction (92%), seizures (58%), and psychiatric symptoms (50%). The authors reviewed data from paraneoplastic serological studies, CSF analysis, MRI and EEG reports. Serum paraneoplastic neuronal antibodies were found in 64% of the patients. Abnormal CSF was found in 78% of patients. The only universal positive finding was that of focal or generalised slowing on EEG, with all 24 patients displaying this.

Two treatment approaches are currently available. Treatment of the underlying cancer with surgery, chemotherapy, radiotherapy, or hormonal treatment may remove the antigen source, and thus antibody production. Although this approach often causes the remission of other neurological paraneoplastic syndromes (e.g. Eaton-Lambert syndrome), the effect on PLE is less successful<sup>6</sup>. The other management approach involves suppression of the immune response with steroids, immunoglobulins, cyclophosphamides, or plasma exchange. Although data is limited, response to this mode of therapy has also been disappointing<sup>3</sup>.

## CONCLUSION

Paraneoplastic limbic encephalitis describes inflammation within the brain's limbic system, resulting from an autoimmune-mediated paraneoplastic process. It is characterised by a sub-acute and severe neurological disorder. The diagnosis is reached primarily from the clinical picture, coupled with supportive investigation and imaging. Negative results do not exclude the disease process. Although PLE is rare, its prevalence is almost certainly more widespread than appreciated. Heightened awareness of this clinical entity will assist earlier diagnosis. Further work is required to improve our understanding of the exact pathophysiology of PLE, and to classify immunological subsets. This may allow more specific targeting of treatments as now occurs in many

other cancer-related disease processes. As this syndrome often precedes overt symptoms of a tumour, awareness of the disease may enable earlier detection of cancers in those patients presenting with sub-acute confusional states caused by a paraneoplastic process.

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