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**Sequential fluctuating paraneoplastic ocular flutter-opsoclonus-myoclonus syndrome and Lambert-Eaton myasthenic syndrome in small cell lung cancer**

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**Abstract**

Paraneoplastic cerebellar degeneration may occur in association with Lambert-Eaton myasthenic syndrome (LEMS), but to our knowledge, the co-occurrence of paraneoplastic opsoclonus-myoclonus syndrome and LEMS has not been previously reported.

A 67-year-old woman presented with a complex partial seizure and evolving ocular flutter, opsoclonus, myoclonus, and 'cerebellar' signs, all of which improved spontaneously within six weeks. Approximately eight weeks after symptom onset, the patient became encephalopathic, she had a further complex partial seizure, and she became areflexic with potentiation of deep tendon reflexes. Radiological, bronchoscopic and histological investigations revealed small cell lung cancer, and neurophysiological investigations confirmed a diagnosis of LEMS. High titre anti-P/Q-type voltage gated calcium channel antibodies were identified in the serum, which increased as the signs of opsoclonus and myoclonus resolved. The encephalopathy and clinical features of LEMS responded dramatically to chemotherapy and radiotherapy.

Spontaneous improvement of paraneoplastic opsoclonus-myoclonus syndrome may occur, and this syndrome may occur in association with LEMS. Anti-voltage gated calcium channel antibodies are not implicated in the pathogenesis of paraneoplastic opsoclonus-myoclonus syndrome.

Paraneoplastic opsoclonus-myoclonus (POMS) syndrome is a rare paraneoplastic syndrome in adults that has been reported in association with a variety of tumours.<sup>1</sup> Anti-neuronal antibodies are only occasionally identified in POMS.<sup>2</sup> Lambert-Eaton myasthenic syndrome (LEMS) may occur in patients with lung neoplasia, and most patients with LEMS will have anti-P/Q type voltage gated calcium channel (VGCC) antibodies in the serum.<sup>3</sup> LEMS may co-occur with other paraneoplastic syndromes, but to our knowledge, has not previously been reported in association with POMS.

### **Case Report**

A 67 year old right handed Caucasian woman had a ten day history of lethargy, a five day history of nausea and vomiting, and a one day history of vertigo, jerky truncal tremor on standing and unsteadiness of gait. She subsequently had a complex partial seizure that prompted referral to hospital. She had had symptoms suspicious of a complex partial seizure six months prior to admission, but did not seek medical attention. There was no other relevant past medical history although she had smoked 40 cigarettes per day for 30 years. On admission, general examination was normal. Neurological examination revealed truncal myoclonus on spinal flexion and on standing, but was otherwise normal. Over the following 3 days, the patient developed increasing nausea, xerostomia and unsteadiness. Further neurological assessment at that stage revealed ocular flutter with occasional opsoclonus, hypometric vertical saccades, saccadic intrusions into pursuit eye movements, and gaze-evoked horizontal nystagmus on right lateral gaze. Intravenous high dose thiamine and multivitamins (pabrinex<sup>®</sup> I and II) were administered twice a day for 5 days, followed by 300 mg of thiamine daily without any clinical response. Over the next two weeks, she developed prominent opsoclonus and upper limb incoordination. The persistent nausea and

truncal myoclonus prohibited any attempt to mobilize. A trial of clonazepam 0.5 mg BD had to be discontinued after two days because of extreme drowsiness; the nausea subsequently responded to treatment with ondansetron and domperidone.

Approximately six weeks after symptom onset, the eye movement abnormalities, ataxia, and truncal myoclonus began to spontaneously resolve. Eight weeks after symptom onset, the patient became encephalopathic and had a further complex partial seizure. Repeat bedside cognitive examination revealed evidence of frontal executive, dominant temporal and mild biparietal dysfunction. Cranial nerve examination, including careful eye movement assessment, was normal. Limb tone and power were normal. There was mild limb and gait ataxia. Deep tendon reflexes were now absent at rest, but there was potentiation following voluntary muscle contraction. Sensory examination was normal. She was then commenced on 200 mg of sodium valproate BD.

Full blood count, ESR, CRP, glucose and calcium were normal. She had intermittent hyponatremia (lowest sodium level 127 mmol/L [normal range 135-145]), with low serum and urine osmolalities consistent with volitional hypervolemia, caused by excessive water intake to relieve her symptoms of dry mouth. Autoantibody screening revealed a positive anti-nuclear antibody titre of  $> 1/1000$  (nuclear membrane and cytoplasmic pattern), but negative anti-double stranded DNA, extractable nuclear antigens, anti-nuclear cytoplasmic antibodies, anti-Ri, anti-Yo and anti-Hu anti-neuronal antibodies, and normal complement levels. High titre serum anti-VGCC antibodies were identified on several occasions:  $446 \pm 60$  (SEM) picomoles/litre (pM) at presentation, rising to  $781 \pm 28$  pM when assayed at the time of development of

areflexia, and  $235 \pm 34$  pM after resolution of the opsoclonus and myoclonus (normal  $< 45$  pM; Figure). MRI of brain with gadolinium revealed minimal small vessel disease in the deep white matter and subcortical regions of both cerebral hemispheres, with no inflammatory changes in the brain stem or cerebellum and no evidence of metastases. Cerebrospinal fluid (CSF) was acellular, with normal protein and glucose, but there was intrathecal synthesis of oligoclonal bands. CSF viral polymerase chain reaction testing was negative for herpes simplex, varicella zoster, cytomegalovirus and Epstein Barr virus. Computed tomography of the thorax showed paratracheal and sub-carinal lymphadenopathy, but no evidence of more widespread disease. Subsequent bronchoscopy revealed an endobronchial lesion, and histological examination of a biopsy specimen confirmed a diagnosis of small cell lung cancer. Mammography was normal. Nerve conduction studies performed after the onset of the areflexia revealed generally small amplitude resting compound muscle action potentials. Repetitive stimulation of the right ulnar nerve was performed at the right wrist with the recording surface electrode on abductor digiti minimi. The initial maximum resting compound muscle action potential amplitude was 7.9mV, which increased to 13mV immediately after sustained maximal isometric contraction for 15 seconds. Single fiber electromyography of right extensor digitorum communis revealed massive jitter and blocking in eight out of nine fiber pairs examined, consistent with a diagnosis of LEMS. Electroencephalogram revealed slowing of the background rhythm, with poorly localized sparse sharp waves over the left more than right hemisphere, but no definite epileptiform changes.

A diagnosis of paraneoplastic opsoclonus-myoclonus syndrome in combination with mild paraneoplastic cerebellar dysfunction and LEMS was established. The patient was then treated with one cycle of single agent etoposide, followed by three cycles of etoposide and carboplatin chemotherapy as standard first line management.

Follow-up assessment two months after completion of chemotherapy revealed a mild reduction in categorical fluency with normal bedside cognitive testing otherwise. Re-examination revealed normal cranial nerves, mild upper limb ataxia, deep tendon reflexes had returned to normal, and she had no myoclonus or other focal limb findings. Repeat CT imaging of thorax showed regression of the thoracic lymphadenopathy, and the patient underwent a course of mediastinal radiotherapy. Seven months after completion of her treatment and twelve months after initial symptom onset, the patient had no residual neurological symptoms or signs. Anti-voltage gated calcium channel antibody titers had fallen to 147 pM, with negative repeat anti-nuclear antibodies. She has remained in remission three years after completion of chemotherapy and radiotherapy.

## **Discussion**

Paraneoplastic opsoclonus-myoclonus syndrome is a rare complication of underlying malignancy in adults which is characterized by the presence of opsoclonus, action myoclonus of limbs, trunk, or head, and occasionally cerebellar dysfunction.<sup>1,4</sup> As the syndrome progresses, encephalopathy and death may subsequently ensue. Resolution of the neurological findings usually requires treatment of the underlying tumour,<sup>1</sup> although spontaneous improvement prior to definitive anti-neoplastic therapy has occasionally been described.<sup>4-7</sup> Furman *et al.* reported two patients with ocular flutter



and cerebellar signs who improved spontaneously before being diagnosed with breast adenocarcinoma and small cell lung cancer, respectively.<sup>6</sup> Nausieda *et al.* described a further patient who developed opsoclonus and cerebellar ataxia without myoclonus in association with an undifferentiated bronchogenic carcinoma.<sup>7</sup> Rapid resolution of the opsoclonus, but not the ataxia, was reported within twenty hours of treatment with 200mg of intravenous thiamine.

In our case, the clinical features of ocular flutter, opsoclonus and myoclonus did not respond to thiamine, but subsequently spontaneously improved, despite evolution of the illness with development of a mild encephalopathy, clinical, neurophysiological and immunological features of LEMS, and occurrence of a second seizure. This suggests that the autoimmune response to presumed neuronal antigens in the mid brain and pons resolved, with subsequent autoimmunity to cortical autoantigens above the brain stem and an increase in anti-VGCC antibody titres. Chemotherapy and subsequent radiotherapy resulted in regression of the lung malignancy as well as resolution of the neurological findings of encephalopathy and LEMS, mirrored by a decrease in anti-VGCC antibody titres.

Paraneoplastic cerebellar degeneration is described in patients with LEMS,<sup>8</sup> but to our knowledge, the co-occurrence of paraneoplastic ocular flutter-opsoclonus-myoclonus and LEMS has not been previously reported. Voltage gated calcium channels are abundant in the cerebellum, and anti-voltage gated calcium channel antibodies have been suggested to play a role in the pathogenesis of paraneoplastic cerebellar degeneration syndromes.<sup>8</sup> POMS has been described in association with a variety of auto-antibodies, including anti-Ri, anti-Hu, anti-amphiphysin, anti-purkinje cell,<sup>1,3</sup>

and anti-mitochondrial antibodies,<sup>9</sup> but has never been reported in association with anti-VGCC antibodies. The fact that the anti-VGCC antibody titres increased as the opsoclonus, myoclonus and ataxia resolved strongly argues against a potential role for these antibodies in the pathogenesis of POMS.

POMS may be associated with an improved prognosis in children with neuroblastoma,<sup>10</sup> and LEMS may be associated with prolonged survival<sup>11</sup> and clinical remission<sup>12</sup> in adults with small cell lung carcinoma. Further follow-up is required to determine whether the co-occurrence of two independent paraneoplastic syndromes, which could confer an enhanced anti-tumour autoimmune response, will impact on the long-term prognosis in our patient who has been in remission for three years following initial chemotherapy. The observation that this lady made a complete neurological recovery following chemotherapy and radiotherapy supports the hypothesis that an unidentified pathogenic paraneoplastic autoantibody interfered with the function of the omnipause neurons in the pons, without irreversible destruction of the neural structures proposed to be involved in the pathogenesis of this movement disorder.

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**Legends for Figure:**

**Figure 1:** Bar chart of anti-voltage gated calcium channel titers (in picomoles of antibody/litre of serum, pM), normal levels < 45pM:

**A,** At the time of presentation with POMS without clinical evidence of LEMS;

**B,** At the time of spontaneous resolution of the opsoclonus and myoclonus but following the development of LEMS;

**C,** Following treatment with chemotherapy and local radiotherapy and resolution of lymphadenopathy on CT thorax

**D,** Nine months after treatment when in clinical remission.

