Opsoclonus-Myoclonus with Multiple Paraneoplastic Syndromes and VGCC Antibodies

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Current evidence suggests that neurological paraneoplastic syndromes are clinical entities in which antibodies directed against tumor epitopes cross-react with native antigens within the nervous system[1,2]. Recent evidence suggests that many antibodies are not exclusively associated with a particular syndrome, and that particular antibodies may be more indicative of the underlying malignancy than a specific neurological disorder[3]. They may serve a protective role in controlling neoplastic growth and spread as the neurological syndrome almost always appears (up to months or years) prior to identification of the underlying tumor[4,5].

Symptomatic paraneoplastic syndromes occur in less than 1% of patients with cancer. However, rates of up to 3-20% have been reported in patients with small cell lung cancer (SCLC), thymomas, and B-cell or plasma-cell malignancies[2,6]. Cases of multiple paraneoplastic syndromes in a single patient are very rare. In this case report we present a patient who concurrently developed Lambert-Eaton Myasthenic Syndrome (LEMS), subacute cerebellar degeneration (SCD), and opsoclonus-myoclonus syndrome (OMS).

Case Report

The patient was a 48-year-old male who initially presented with a raised nodular lesion on the anterior aspect of his right leg. Biopsy revealed a well-differentiated superficially invasive squamous cell carcinoma. The lesion was excised using wide margins and a split thickness skin graft. He had an uncomplicated initial post-operative recovery but within a few months noticed ongoing weight loss (approximately 15 kg since the operation), shortness of breath and fatigue. He sought medical attention and a mass was identified on the right side of his neck. A computed tomogram (CT) scan demonstrated a right-sided supraclavicular mass, a right upper lobe mass, and bilateral hilar lymphadenopathy. Biopsy of the right supraclavicular mass revealed limited stage SCLC. Computed tomography of the brain and magnetic resonance imaging of the spine were normal. He received a three-day course of chemotherapy with etoposide (100mg/m^2) and cisplatin (25mg/m^2). Three months following chemotherapy he received prophylactic whole brain irradiation.

Six months later he acutely developed nausea, vomiting, and vertigo. He was admitted to his local hospital and diagnosed with vestibular neuronitis. Over the next two weeks he complained of double vision, visual blurring and "jumping", and difficulties swallowing. He reported significant problems with limb incoordination. He did not describe sensory changes, dry mouth or other autonomic symptoms. The attending physicians reported nystagmus, dysarthria, hypophonia, myoclonus, and ataxia on exam. Computed tomogram of the brain was reported as normal. Given the rapid progression of symptoms and lack of response to treatment (betahistidine, dexamethasone, and ondansetron), he was transferred to the Queen Elizabeth II Health Sciences Centre for further investigations.

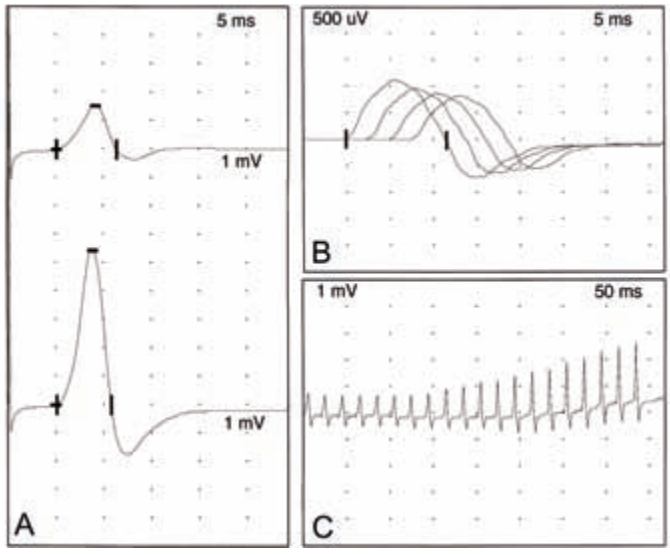

Figure: *A) A supramaximal stimulus was given to the tibial nerve at the ankle recording over the abductor hallucis muscle. The top trace was before exercise and the bottom trace immediately after a ten second tetanic contraction of the muscle. B) A supramaximal stimulus was given at 2 Hz to the right peroneal nerve at the knee recording over the anterior tibial muscle. The decrement between the 1st and 4th CMAP responses was 25%. C) A supramaximal stimulus was given at 50 Hz to the ulnar nerve recording over the hypothenar muscle. Twenty responses were recorded demonstrating an incremental response of 183%.*

On transfer he was no longer able to ambulate because of severe imbalance. Examination of the cranial nerves revealed bilateral opsoclonus, ocular ataxia, right-beating nystagmus on right gaze and dysarthric staccato speech. Motor exam revealed

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generalized mild muscular atrophy and myoclonus, but extremity strength was not significantly reduced. He was areflexic with flexor plantar responses. Bilateral intention tremor was present. Dysmetria was observed on finger-to-nose testing and heel-to-shin testing. Rapid alternating movements were impaired. Sitting balance was impaired with a propensity for falling to the left side. Romberg and gait could not be tested because of profound ataxia.

Complete blood count revealed a normocytic anemia (Hemoglobin = 112 g/L, Mean cell volume = 93.3 fL). Electrolytes, renal and liver function tests, thyroid stimulating hormone, free thyroxine, vitamin B_{12} and folate were normal. Erythrocyte sedimentation rate (40 mm/HR) and C-reactive protein (9.22 mg/L) were elevated. Anti-nuclear and extractable nuclear antibodies (dsDNA, chromatin, ribosomal P, SS-A/Ro, SS-B/La, centromere B, Sm, Sm/RNP, Scl-70, and Jo-1) were negative. Rheumatoid factor was not detected. Complement levels (C3 and C4) were normal. Unenhanced and gadolinium-enhanced MRI sequences of the brain revealed cerebellar atrophy. Thoracic CT did not reveal definitive evidence of a neoplasm. 2-fluoro-2-deoxy-D-glucose positron emission tomography scanning was not available for patient assessment.

Nerve conduction studies revealed diffusely small compound muscle action potential (CMAP) amplitudes ranging from 12 to 88% of the lower limit of normal. All other motor nerve conduction parameters and F wave latencies were normal. Sensory nerve conduction parameters were normal. An EMG was requested to assess whether neuropathy was contributing to the ataxia. The evaluation was not suggestive of a demyelinating polyneuropathy or sensory neuronopathy as a cause for this problem. As small CMAP amplitudes were the only abnormality on routine studies, LEMS was considered and studies with brief tetanic exercise as well as repetitive nerve stimulation were performed. A ten second tetanic exercise produced increment of the CMAP amplitude in the right median (117%), tibial (243%), peroneal to anterior tibial (70%) and ulnar (575%) nerves (Figure A). Repetitive stimulation (2 Hz) of the ulnar nerve recording over the hypothenar eminence and the peroneal nerve recording over the anterior tibial muscle revealed significant decrement (range 25 to 37%) (Figure B). Repetitive stimulation at 50 Hz revealed a 183% increment after 20 stimuli in the right ulnar nerve when recording over the hypothenar eminence (Figure C). Needle electromyography revealed small motor unit potentials with moment-to-moment variation in configuration suggestive of a neuromuscular junction defect. The electrodiagnostic changes were consistent with a presynaptic neuromuscular junction disorder, with features typical of LEMS.

Paraneoplastic antibodies were assessed at the Mayo Medical Laboratories using immunofluorescence, enzyme-linked immunosorbant assay, radioimmunoprecipitation, and western blot analysis. P/Q-type calcium channel antibodies were detected at a titre of 0.14 nmol/L (negative ≤ 0.02 nmol/L). Additional antibodies associated with subacute cerebellar degeneration (PCA-Tr, PCA-1/anti-Yo, PCA-2, AGNA-1, ANNA-1/anti-Hu, CRMP-5-IgG), opsoclonus-myoclonus (anti-Ri/ANNA-2), and other paraneoplastic syndromes (amphiphysin antibody, ACh receptor [muscle] binding antibody, striational [striated muscle] antibody, N-Type calcium channel antibody, ANNA-3, AChR ganglionic antibody, neuronal antibody, and neuronal (V-G) K+ antibody) were not detected.

The patient was diagnosed with concurrent LEMS, SCD, and OMS. Chemotherapy was not indicated given the lack of convincing radiological evidence of recurrent cancer. The patient was treated with intravenous immunoglobulin (0.4g/kg/d) for five days. Pyridostygmine (30 mg po tid) and 3,4-diaminopyridine (20 mg po qid) were used to control LEMS-related symptoms. A percutaneous gastrostomy tube was ultimately required. The patient responded well to therapy but still required a wheelchair due to residual ataxia at the time of discharge.

Discussion

Neurologic paraneoplastic syndromes are relatively rare conditions. Multiple simultaneous syndromes have been previously reported in only a few patients[7-10]. To our knowledge, concurrent OMS, SCD, and LEMS have not been reported. Anti-P/Q calcium channel antibodies have been reported in both LEMS[11-17] and SCD[12,18-20] and in cases of concomitant LEMS and SCD[12,21-24] but not in OMS. A recently identified paraneoplastic antibody, anti-glial nuclear antibody, was included as a part of the screen[25]. This autoantibody targets the nuclei of Bergmann glia located in the cerebellum. Specifically, it reacts with SOX1, a highly immunogenic tumor antigen expressed by SCLC[26]. Its presence has been associated with LEMS in the context of SCLC but was not detected in the serum of our patient[25,26].

Our ability to detect residual or recurrent tumor would have been improved with access to positron emission tomography scanning. A recent retrospective review of 104 patients with suspected paraneo-plastic syndrome demonstrated improved neoplastic detection rates with positron emission tomography scanning (8/10 pathologically confirmed malignancies detected) compared to CT scanning (3/10 pathologically confirmed malignancies detected). Sensitivity, specificity, positive predictive value, and negative predictive values were 80%, 67%, 53%, and 88% respectively[27].

The patient's cerebellar degeneration was unlikely to be related to radiation. Current data suggests that there is no significant difference in neuropsychological outcomes or in the rate of CT brain abnormalities detected between patients with SCLC who were treated with prophylactic whole brain irradiation compared to those who were not treated[28].

The etiology of the patient's OMS remains undetermined. It is possible that one antibody may cause multiple neurological paraneoplastic syndromes. Animal models suggest that P/Q VGCC knock-out mutations (CACNA1A gene) result in subnormal gains with high-frequency stimuli in tests of the angular vestibuloocular reflex. Minimally reduced gains were recorded in horizontal optokinetic responses[29]. Likewise, excessive intracellular calcium, as suggested by decreased sarcoplasmic reuptake rates, has been postulated as a pathophysiological mechanism in primary inferior oblique over-activation[30]. However, mutations in the CACNA1F gene (which codes for the α1-subunit of the L-type voltage gated calcium channel [VGCC]) are associated with nystagmus as a part of incomplete congenital stationary night blindness syndrome[31]. However, a specific paraneoplastic antibody is not found in the majority of patients presenting with acquired OMS[32]. Thus it remains unclear as to what role, if any, anti-VGCC antibodies would play in opsoclonus.

Squamous cell carcinomas rarely produce neurological paraneoplastic syndromes. In our patient the SCLC was probably responsible for inducing antibody production given its frequent association with neurological paraneoplastic disorders and the timing of the paraneoplastic symptoms in relation to the diagnosis of lung cancer. Small cell lung carcinoma is correlated with the presence of anti-VGCC antibodies[33]. Anti-VGCC antibodies block inward calcium currents in SCLC cell lines[34] and their presence improves disease prognosis[35]. There are also associations between LEMS and central nervous system paraneoplastic disorders, an observation supported by the presence of antibodies in CSF of some patients with combined SCD, LEMS, and SCLC[17,18,22].

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