Polymyoclonus, Laryngospasm, and Cerebellar Ataxia Associated With Adenocarcinoma and Multiple Neural Cation Channel Autoantibodies

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Objective: To describe and provide audiovisual documentation of a syndrome of polymyoclonus, laryngospasm, and cerebellar ataxia associated with adenocarcinoma and multiple neural cation channel autoantibodies.

Design: Case report with video.

Setting: University hospitals.

Patient: A 69-year-old woman presented with subacute onset of whole-body tremulousness and laryngospasm attributed to gastroesophageal reflux.

Results: Further evaluation revealed polymyoclonus, cerebellar ataxia, and laryngospasm suspicious of an underlying malignant neoplasm. Surface electromyography of multiple limb muscles confirmed the presence of polymyoclonus. The patient was seropositive for P/Q-type voltage-gated calcium channel antibody; subsequently, whole-body fluorine 18 fluorodeoxyglucose positron emission tomography and cervical lymph node biopsy revealed widespread metastatic adenocarcinoma. Follow-up serologic evaluation revealed calcium channel antibodies (P/Q type and N type) and potassium channel antibody.

Conclusions: We highlight the importance of recognizing polymyoclonus. To our knowledge, this is also the first description of a syndrome of polymyoclonus, laryngospasm, and ataxia associated with adenocarcinoma and these cation channel antibodies.

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REPORT OF A CASE

A 69-year-old woman was diagnosed with “action tremor,” which began in her hands in June 2007. She had a history of smoking (45 pack-years), diabetes mellitus for 10 years (she was receiving insulin for 2 years), treated hypothyroidism, and uterine cancer treated 2 decades earlier with hysterectomy and oophorectomy without subsequent recurrence. Since May 2007, she had daily self-resolving episodes of laryngospasm, each lasting 30 to 60 seconds, with difficulty breathing, stridor, choking, and coughing; this was initially attributed to gastroesophageal reflux. The tremulousness progressed over a few weeks to involve both legs, and she became unsteady and started falling. By October 2007, she was ambulating with a walker. She also had twitches of the face and tongue, and her speech became mildly slurred. Clonazepam, 1 mg daily, initially reduced the involuntary movements, but this effect quickly waned. She had reduced appetite, with weight loss of 5 to 10 kg. She had no prior exposure to psychotropic medications, and her family history was negative for neurologic disorders.

MULTIFOCAL, REPE-
Examination in October 2007 showed jerky tremulousness (polymyoclonus) involving the limbs and perioral region (video 1, http://www.archneurol.com). This was present at rest as well as during posture and action, and it was not exacerbated by tactile stimulation or noise. There was no evidence of cognitive dysfunction, apraxia, or cortical sensory loss. Frontal release and Myerson signs were absent. Finger-nose coordination was normal, but there was mild heel-shin ataxia and moderate gait ataxia. There was no parkinsonism. Results of the rest of the neurologic examination, including eye movements, limb power, tendon reflexes, and plantar responses, were unremarkable.

Surface electromyography of multiple limb muscles confirmed the presence of polymyoclonus with 10- to 40-millisecond bursts, without evidence of myoclonus (Figure). The myoclonus increased with action and was more prominent in the hand (first dorsal intersosseous muscle) than in the forearm, proximal arm, or leg muscles. The jerks were too frequent to use jerk-locked back averaging. There was no exaggerated response to cutaneous stimulation and the amplitude of the N20 peak of the median nerve somatosensory evoked potential was normal. Results of nasopharyngoscopy including vocal cord examination by an ear, nose, and throat surgeon were normal. Video swallow evaluation results were also normal, with no evidence of aspiration. Results of a nerve conduction study, needle electromyography, repetitive nerve stimulation, and contrast brain magnetic resonance imaging were normal. Results of spinal fluid analysis including oligoclonal bands were normal except for mild protein level elevation (52 mg/dL). The patient underwent an extensive serologic and cerebrospinal fluid evaluation for antibody markers of neurologic autoimmune and cancer in the Neuroimmunology Laboratory, Mayo Clinic, Rochester, Minnesota. Her serum and cerebrospinal fluid were evaluated by standardized immunofluorescence criteria for IgG neural autoantibodies (antineuronal nuclear antibody 1, 2, and 3; amphi- physin antibody; Purkinje cell antibody 1, 2, and Tr; collapsin response-mediator protein 5; and antiglial/neuronal nuclear antibody 1, 2, and 3).3,4 Her serum was also evaluated by radioimmunoprecipitation assays for neuronal voltage-gated cation channel (voltage-gated calcium channel [VGCC] [P/Q type and N type] and voltage-gated potassium channel [VGKC]), muscle and neuronal gangli- onic (α3) nicotinic acetylcholine receptor, and glutamic acid decarboxylase 65 isoform antibodies and by recombinant Western blot for collagen response-mediator protein 5 IgG.6 P/Q-type VGCC antibody was detected at a value of 0.15 nmol/L (reference range, ≤0.02 nmol/L). Serum antibodies to glutamic acid decarboxylase 65 isoform (0.16 nmol/L [reference range, ≤0.02 nmol/L]) and thyroid peroxidase (26.4 IU/mL [reference range, <9.0 IU/mL]) were also detected.

Body computed tomography revealed a 2-cm subcortical lymph node and several mildly enlarged paratracheal and suprahilar lymph nodes. Mammography and abdominopelvic (transvaginal) ultrasonography results were unremarkable. Whole-body fluorine 18 fluorodeoxyglucose positron emission tomography showed widespread areas of abnormal uptake in the thyroid gland and lymph nodes in the chest (subcarinal, paratracheal, and para-aortic). Bronchoscopy results were normal, but cervical lymph node biopsy confirmed metastatic adenocarcinoma most likely originating in lung.

Intravenous immunoglobulin therapy was initiated in November 2007 (0.4 g/kg daily over 5 days), with further courses (1 g/kg) given in December 2007 and January 2008. The improvements in her polymyoclonus and laryngospasm were dramatic but not sustained. Paclitaxel and carboplatin chemotherapy initiated in January 2008 resulted in more durable improvement. An examination was performed a few days after completion of her third course of chemotherapy in March 2008 (video 2). Polymyoclonus was minimal (on a slightly lower dosage of clonazepam, 0.75 mg/d) and episodes of laryngospasm had become very infrequent. She reported no further falls, but gait ataxia did not appear to be significantly different compared with the initial assessment. Weight loss had stabilized. Her condition remained stable in the following months (last follow-up in December 2008). Repeat serologic evaluation revealed 2 previously undetectedcation channel antibodies. These were N-type VGCC antibody (0.05 nmol/L [reference range, ≤0.02 nmol/L]) and VGKC antibody (0.16 nmol/L [reference range, ≤0.02]). P/Q-type VGCC antibody was again detected, with a reduction in value from the initial evaluation (0.05 nmol/L).

COMMENT

The multifocal, repetitive, low-amplitude jerks of polymyoclonus may give a superficial impression of tremor, but irregular or jerky twitches on closer inspection should serve as a red flag. Neurophysiologic analysis is confirmatory and demonstrates irregular muscle bursts shorter than 50 milliseconds.7 Although the origin of myoclonus in our patient could not be determined with certainty, the brief electromyographic burst duration and the predominance of myoclonus in the hand are suggestive of a cortical origin. To our knowledge, the anatomic substrate within the central nervous system of paraneoplastic myoclonus has not been investigated previously.
Cation channel antibodies are typically associated with small-cell lung carcinoma, but have also been associated with lung adenocarcinoma, ovarian and breast carcinoma, and even vocal cord epidermoid carcinoma. It is possible that this patient had a cancer of heterogeneous lineage (including small cell carcinoma) that was not detected, in addition to adenocarcinoma. Although she was found to have P/Q-type VGCC antibody initially, subsequent evaluation revealed a broader profile including N-type VGCC and VGKC antibodies. Serologic evaluation of patients with suspected paraneoplastic neurologic disorders is frequently enhanced by comprehensive screening for cancer-specific autoantibody profiles.

The VGCC antibodies have been linked to a range of paraneoplastic neurologic syndromes including Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration, encephalomyelitis, and sensory neuronopathy. Protean neurologic manifestations have been reported with VGKC antibody, cognitive impairment and seizures being most common. To our knowledge, a neurologic syndrome including laryngospasm has not been described previously in association with these cation channel antibodies. The spectrum of neurologic manifestations associated with paraneoplastic antibodies commonly broadens after initial description, and paraneoplastic neurologic manifestations of cancer are typically multifocal.

The presence of glutamic acid decarboxylase 65 isoform and thyroid peroxidase antibodies in our case likely reflects coexisting diabetes and autoimmune thyroid disease, respectively. The glutamic acid decarboxylase 65 isoform antibody is commonly seen in type 1 diabetes mellitus, but very high values (typically >100-fold higher than those found in diabetes) are rarely associated with a variety of autoimmune neurologic disorders including cerebellar ataxia, seizures, brainstem and spinal cord disorders, and stiff person syndrome.

The response to treatment in this case is consistent with prior reports describing variable response of myoclonus and laryngospasm to immunotherapy and minimal or no response in ataxia, probably because of irreversible Purkinje cell loss.

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Author Contributions: Dr Lim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lim and Lang. Acquisition of data: Lim, Mason, Young, Chen, Bower, McKeon, Pittock, and Lang. Analysis and interpretation of data: Lim, Mason, Young, Chen, Bower, McKeon, Pittock, and Lang. Drafting of the manuscript: Lim. Critical revision of the manuscript for important intellectual content: Lim, Mason, Young, Chen, Bower, McKeon, Pittock, and Lang. Administrative, technical, and material support: Lang. Study supervision: Lim and Lang.

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REFERENCES