Paraneoplastic Isaacs syndrome leading to diagnosis of small-cell lung cancer

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Paraneoplastic Isaacs syndrome is a rare disorder with distinct clinical and electromyographic characteristics. It is a consequence of neoplastic process that is not directly caused by the tumor itself, but usually mediated by immune response primarily against the tumor and neural tissues are damaged owing to bystander effect. Paraneoplastic neurologic disorders may precede cancer diagnosis. Here we report the case of 75-year-old woman who presented with numbness, tingling sensation, and weakness of lower extremities, and was diagnosed with Isaacs syndrome and subsequently small-cell lung cancer. Plasmapheresis and treatment of small-cell lung cancer produced significant symptoms improvement. We also conduct a complete review of the published case reports and case series of Isaacs syndrome of paraneoplastic etiology (Table), which usually has good response to carbamazepine and to specific treatment of underlying neoplasm.

Case presentation and summary

A 75-year-old woman with a past medical history of hypertension and hyperlipidemia presented to the neurology clinic. Initially she had numbness and tingling sensation of all extremities followed by weakness of the lower extremities that started in the distal parts and progressed proximally. She had also lost the ability to write and was not able to carry out her activities of daily living.

Eight years before presentation, she had been evaluated for peripheral neuropathy that started abruptly on the left side of the body. She had magnetic resonance imaging (MRI) of the brain, which demonstrated chronic small-vessel ischemia with microinfarcts. She subsequently underwent right carotid endarterectomy; however, her paresthesia had progressed and further work-up showed IgM lambda monoclonal gammopathy without IgM elevation. Electromyography (EMG) showed mild sensory axonal neuropathy in addition to a mild left L5 radiculopathy. Her monoclonal gammopathy had resolved on subsequent visit. She had unremarkable colonoscopy a year before presentation. Her home medications included amlodipine, hydrochlorothiazide, omeprazole, aspirin, and metoprolol. She had history of 50 pack-years of smoking and had quit 8 years before presentation.

Physical examination revealed percussion myotonia (delayed relaxation) of the left hand, myotonia of the tongue, inability to release the handgrip, decreased pinprick sensation and proprioception, and decreased strength in the lower extremities. Deep tendon reflexes of biceps, triceps, quadriceps, and Achilles were 1+ bilaterally, denoting very slight reflex detected or detected only with reinforcement. Her complete blood count and complete metabolic profiles were within normal range. Serum and urine electrophoresis were negative for monoclonal protein. Vitamin B12 and thyroid-stimulating hormone levels were also normal. A computed-tomography (CT) scan of the brain was normal. An cerebrospinal fluid (CSF) analysis showed very mild elevation of protein (51 mg/dL), with 2 nucleated cells/μL (all were lymphocytes). CSF IgG index was 0.46, with no oligoclonal band identified. An EMG demonstrated the presence of neuromyotonia and myokymic discharges in the first dorsal interosseus, foot interossei, tibialis anterior, and vastus lateralis, consistent with Isaacs syndrome. Voltage-gated potassium channel antibody was negative. The patient also had vesicular rash on dermatome C6-7, consistent with varicella zoster reactivation and for which she was started on a course of valacyclovir 1,000 mg tid for 10 days. She was hospitalized for profound weakness such that she was not able to walk or care for herself. Her motor symptoms improved after a week of hospi-

Accepted for publication December 16, 2015. Correspondence: Grerk Sutamtewagul, MD; grerk-sutamtewagul@uiowa.edu. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2016;14(12):522-527. doi:I 10.12788/jcso.0230.

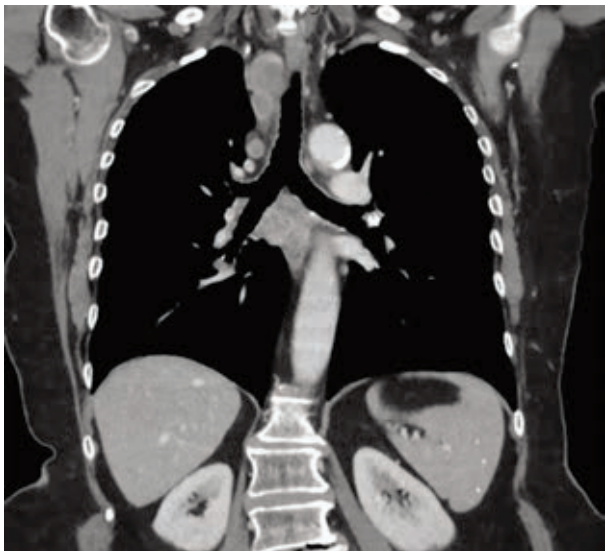

FIGURE 1 Initial computed-tomography scan revealing multiple hilar and mediastinal lymphadenopathy.

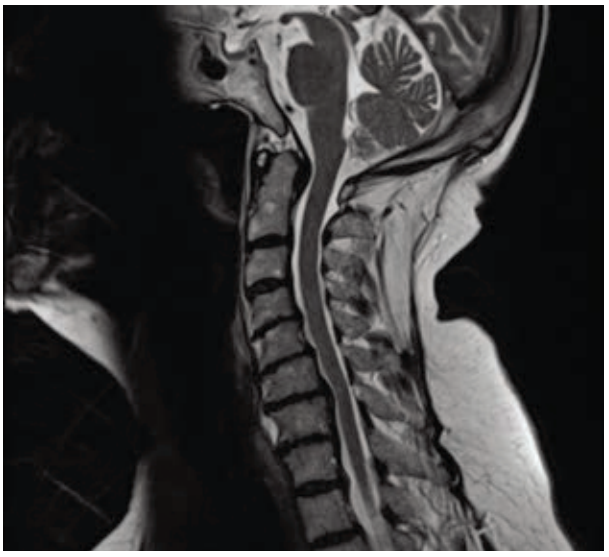

FIGURE 2 Magnetic resonance imaging of the C-spine was negative for cervical myelopathy.

talization along with sensory symptoms after initiation of gabapentin with titration up to 1,800 mg a day, and was later changed to pregabalin 150 mg bid due to persistent post-herpetic neuralgia.

A CT scan of the chest, abdomen, and pelvis obtained for malignancy screening demonstrated a 10 x 8 mm right lung nodule with right hilar adenopathy and multiple enlarged mediastinal lymph nodes (Figure 1). Bronchoscopy revealed bilateral diffuse thickening of bronchial mucosa and 2 fungating masses in the trachea. Endobronchial ultrasound with biopsy was done. Pathology revealed small-cell carcinoma from the right level 4 lymph node aspiration specimen. MRI of thoracic spine also showed complete marrow replacement of T9 vertebral body, but MRI of the brain was negative for metastasis (Figure 2). She was diagnosed with extensive stage small-cell carcinoma. Chemotherapy with carboplatin (AUC 3) and etoposide (100 mg/m^2) was started. She was in the hospital for 7 days and released when she had a marked improvement in strength and was able to walk some and do some self-care.

A month after discharge, she experienced worsening of her weakness and paresthesia. Screening for anti-neuronal nuclear antibodies and Purkinje cell cytoplasmic antibody were negative. Plasma exchange was initiated and resulted in significant improvement in her strength; however, the effect lasted about 4 weeks and plasma exchange was repeated. Carbamazepine 100 mg bid was initiated to help relieve her neurological symptoms; but she did not tolerate the medication due to presyncope symptoms.

She completed 4 cycles of carboplatin and etoposide, but the treatment was complicated by her multiple hospitalizations with fever and abdominal pain. Subsequent chest CT imaging showed good response to the carboplatin and etoposide regimen with significant improvement in myotonia and, to a lesser extent, paresthesia. The disease recurred after 4 months after the completion of her last cycle of chemotherapy, as evidenced by a CT scan and confirmed with transbronchial biopsy. Second-line chemotherapy with topotecan was discussed but deemed too toxic. She opted to pursue palliative radiation to the chest. Brain metastasis was noted just before the initiation of radiation treatment. She received thoracic and whole brain radiation (3950 cGy/16 fractions and 3000 cGy/10 fractions, respectively). The patient subsequently developed multilobar pneumonia and died of hypoxic respiratory distress and septic shock, 7 months after diagnosis of small-cell lung cancer.

Discussion

Hyam Isaacs, a South African neurologist, described 2 cases with a syndrome of continuous muscle fiber activity.[1] Needle EMG of both patients showed a similar pattern of constant rapid dysrhythmic discharge of independent muscle fibers that worsened with voluntary movement. Phenytoin was found to relieve the symptoms and led to significant improvement of muscle power of both cases, suggesting that the defect may be at the peripheral nerve cell membrane. The syndrome was sometimes defined as acquired neuromyotonia (continuous muscle activity arising from peripheral nerve).[2] However, the mechanism behind the pathogenesis was not elucidated until it was suggested by Bostock and Baker[3] that human motor axon also possesses a slow potassium channel that is directly related to threshold electrotonus, which might explain neuromyotonia. Several associations of neuromyotonia

TABLE Review of case reports and case series with paraneoplastic Isaacs syndrome

Author	Year	Patient description	Neoplasm description/histology	VGKC Ab	Treatment	Outcome
Waerness[16]	1974	70 M with stiffness and cramps in the legs	Malignant lung carcinoma	-	Cobalt irradiation, Bleomycin dosage?, Diphenylhydantoin 400 mg/day, Carbamazepine 600 mg/day	Improved with remaining right thigh stiffness
Walsh[17]	1976	48 F with increasing muscular rigidity	Mediastinal tumor, unknown pathology, possible bronchogenic carcinoma by history	-	Diphenylhydantoin 100 mg TID	Improved muscle stiffness in 4 days, able to walk in 2 weeks
Partanen[18]	1980	57 M with weakness of the legs and gait disturbance	Carcinoma parvocellularis (small-cell carcinoma) of mediastinum, later developed brain metastasis	-	Diazepam Diphenylhydantoin Carbamazepine 300 mg daily	Good initial response No response Decreased stiffness and signs of tetany
Rossi[19]	1990	57 M with weakness, muscle stiffness and twitching of lower limbs	Right apical lung tumor: ex cicatrix adenocarcinoma; middle/lower lobe: bronchioloalveolar carcinoma; later developed anaplastic solid cell renal carcinoma	-	Carbamazepine 600 mg/day	Spontaneous leg movement disappeared
Perini[20]	1994	51 M with MG and thymoma treated with thymectomy presented with dysesthesia and muscle twitching of the face 1 year after surgery	Thymoma	-	Phenytoin	Improvement of symptoms
Zifko[21]	1994	65 M with muscle cramp and fasciculation in both legs	IgM lambda plasmacytoma and IgM paraproteinemia	-	Carbamazepine	Response
Gutmann[22]	1996	68 F with muscle fatigue and continuous muscle twitching	IgG kappa paraproteinemia with muscle amyloidosis	-	No therapy	Stable disease
Caress[23]	1997	38 F with spasm and cramps of hand and forearms	Hodgkin lymphoma (7-cm anterior mediastinal mass)	-	Phenytoin ABVD	Complete resolution of neurological symptoms
Toepfer[24]	1999	50 M with progressive muscle stiffness and sudden brief involuntary limb movement	Small-cell lung carcinoma	Negative (anti-Hu positive)	Carboplatin, etoposide, and vincristine	Complete resolution
van den Berg[25]	1999	48 M with painful paresthesia, hyperhidrosis, muscle twitching, and urinary retention	Thymoma, mixed type, stage IVA	Negative	Radiotherapy and plasma exchange	Complete resolution
Hayat[26]	2000	68 M with burning paresthesia of distal arms and legs, "worm-like" muscle movement	Malignant thymoma	-	Surgical resection of thymoma and radiation Plasma exchange	Worsening Improved; Eventually died of metastatic disease
Benito-Leon[27]	2000	68 M with muscle cramps	Essential thrombocythemia	Negative	Hydroxyurea Phenytoin 200 mg/day Carbamazepine 600 mg/day	No neurological response Partial response Complete resolution
Mygland[28]	2000	Case series of 6 patients: 29 M, 52 M, 55 M, 70 M, 54 F, M of unknown age	Thymomas (2 cortical, 1 carcinoma, 1 mixed, 1 atypical carcinoid, 1 unknown type)	Positive (4/6)	Unknown	Unknown

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Lahrmann[29]	2001	59 F with paresthesia of upper extremities and trunk and uncertainty in fine motor, followed by inability to walk	History of Hodgkin lymphoma with relapse 4 years prior initiation of neurologic symptoms	Negative	Carbamazepine	Complete resolution
Hart[30]	2002	Series of 60 patients with PNHE with 42 had Isaacs syndrome (12 patients considered paraneoplastic)	6 patients with thymoma with MG 2 patients with thymoma without MG 3 patients with small-cell carcinoma 1 patients with lung adenocarcinoma	Positive (6/8 thymoma-related)	-	-
Viallard[31]	2005	50 F with abdominal pain and progressive muscle cramps and twitching	Thymoma type B3	Positive	Plasma exchange	Improvement of abdominal symptoms
Evoli[32]	2007	Review of 260 cases of thymoma patients; 6 patients with Isaacs syndrome	Thymoma	-	-	-
Canovas[33]	2007	48 M with bilateral leg weakness and undulating movement	Clear cell renal carcinoma	-	Carbamazepine Tumor resection	Resolution of neuromyotonia after tumor resection
Eimil-Ortiz[34]	2009	66 F with intense cramps in extremities and abdomen for 2 months	Oncocytic tumor of the thyroid	Positive	Carbamazepine Tumor resection	Resolution of cramps
Forte[35]	2009	76 M sensory disturbance of lower limbs and progressive muscle stiffness, twitching	Invasive high-grade transitional cell carcinoma of urinary bladder	Positive	Phenytoin, Carbamazepine Tumor resection	Slight improvement Complete resolution
Paul[36]	2010	65 M with severe paresthesia both feet, painful muscle cramps and hyperhidrosis, previous diagnosis of MG	Thymoma type B3	-	Thymectomy	Complete resolution
Issa[37]	2011	59 F with twitching of face, fingers and toes, episodic muscle tone loss	Stage IC, grade 3, clear-cell ovarian carcinoma	Negative	Gabapentin/ prednisone Acetazolamide 1000 mg daily Tumor resection followed by cisplatin and paclitaxel	No response Improved twitching Complete resolution
Rana[38]	2012	64 M with blepharospasm, slurred speech, neck and face stiffness	Lymphoplasmacytic lymphoma	Negative	Rituximab	Died of sepsis and thromboembolism
		65 M with weakness in both legs, muscle twitching and cramping	Spinal cord hemangioblastoma 5 years after neurological symptom started	Positive	Carbamazepine and resection of tumor	Complete resolution
Özçakar[39]	2012	65 M with lower extremities muscle contraction and hyperhidrosis	Malignant thymoma	-	Surgical resection of the tumor and radiation	Complete resolution
Fleisher[40]	2013	53 M with involuntary muscle twitching, history of MG and stage II malignant thymoma	Recurrent thymoma	Positive	Phenytoin, Lacosamide Cisplatin/Doxorubicin	Not improved Improved, later died of sepsis
Tsivgoulis[41]	2014	59 M with progressive muscle weakness, twitching, cramps, hyperhidrosis	Epithelioid thymoma type B3	Negative (ANNA positive)	Surgical resection	Complete resolution
Dardiotis[42]	2015	70 M with muscle twitching, spasm, and hyperhidrosis	Metastatic small-cell carcinoma	Positive	Carbamazepine Chemotherapy	Ineffective Died from complication

AVBD, doxorubicin, bleomycin, vinblastine, dacarbazine; M, male; F, female; MG, myasthenia gravis; PNHE, peripheral nerve hyperexcitability; VGKC Ab, anti-voltage-gated potassium channel antibody

with autoimmune conditions such as myasthenia gravis and celiac disease were reported[4]. Sinha[5] reported a case of neuromyotonia who had significant improvement in symptoms with plasma exchange. Purified IgG of the patient was passively transferred to mice, producing resistance to d-tubocurarine at the neuromuscular junction, along with observed decrease in mice activity. Further cellular electrophysiologic study of mice motor neuron preparation indicated increased presynaptic nerve-terminal membrane excitability, which is known to be related to slow potassium channel. Voltage-gated potassium channel (VGKC) is usually concentrated around the paranodal and terminal region of myelinated axon.[6] Hart and colleagues demonstrated that patients with acquired neuromyotonia exhibit autoantibodies against various types of VGKCs, establishing the pathophysiologic basis of the disease.[7]

Autoantibodies to VGKC are not only implicated in peripheral nerve diseases as in Isaacs syndrome, but also in central nervous system disease such as limbic encephalitis. Patients with Morvan syndrome develop both central (mostly autonomic) and peripheral nervous system pathology from antibody to VGKC and tend to have greater proportion of paraneoplastic etiology.[8]

Isaacs syndrome is rare with prevalence expected to be less than 1 in 100,000. There is male predominance in this syndrome, with the male:female ratio at around 1.8:1 in 2 case series,[9,10] and as extreme as 19:1 in a series.[11] It is associated with both autoimmune disorders and can be nonimmune-mediated.[4] The reported autoimmune disorders include paraneoplastic syndrome, myasthenia gravis, diabetes mellitus, chronic inflammatory demyelinating neuropathy, Guillain-Barré syndrome, Addison disease, celiac disease, pernicious anemia, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, and so on. Association with possible non-immune mediated conditions includes toxins (insecticide, alcohol, venom) and potassium-channel gene mutations.

Our patient presented with weakness and paresthesia, which are not typical presentation of the disease.[4] Most patients with Isaacs syndrome usually complain of muscle cramps and twitching.[2] Distal sensory loss occurs in only minority of the patients. Physical examination of our patient revealed relaxation myotonia, which is seen in around one third of patients with this syndrome (pseudomyotonia). The patient's EMG finding was consistent with neuromyotonic and myokymic discharge, both of which are prominent features of Isaacs syndrome. Neuromyotonic discharge is caused by hyperexcitability of single motor axon of peripheral nerve and has specific characteristics on EMG described as doublet, triplet, or short bursts of high intraburst frequency (30-300 Hz) single motor unit (or partial motor unit) discharge, producing a short, high-pitched "ping" sound from the EMG machine.[12] Myokymic discharge is the regular or irregular discharge of groups of motor units causing flickering of the muscle. EMG can differentiate myokymia from fasciculation and myoclonus by its characteristics of lower frequency (2-60 Hz) doublets, triplets, or multiplets in short rhythmic burst of motor unit action potential, followed by a silence and recurrence of the burst at regular intervals.

As evident in many other paraneoplastic syndromes, Isaacs syndrome usually improves after specific treatment of an underlying malignancy. Plasma exchange was also shown to significantly improve our patient's muscle weakness even though the effect was not long lasting. This treatment strategy is supported by case reports[13,14] and a practice guideline.[15] Plasma exchange usually results in a decrease in anti-VGKC antibody titer and clinical improvement that lasts around 6 weeks. The role of immunosuppressive agents is not well established.

Symptomatic treatment with phenytoin, carbamazepine, lamotrigine, and valproate or combinations of these agents has been reported to improve symptoms.[15]

We reviewed 49 cases of paraneoplastic Isaacs syndrome published in case reports or case series in English or Spanish. Of the 30 patients with available data, the age range is 29-76 years (median, 59 years). Of 31 patients with available gender data, 23 of them are men (2.9:1, male:female ratio). Twenty-six patients had VGKC antibody tested, and 16 (61.5%) were positive. The clinical implication of positive antibody is difficult to determine owing to the lack of data; however, from case reports with reported outcomes, VGKC antibody positivity does not seem to affect the response to treatment or clinical outcome. The most common neoplastic process associated with Isaacs syndrome is thymoma (25 of 49 patients, 51.0%), followed by small-cell carcinoma (6 patients, 12.2%). Other reported neoplastic processes include bronchogenic carcinoma, renal cell carcinoma, bladder carcinoma, ovarian carcinoma, oncocytic tumor of the thyroid, spinal cord hemangioblastoma, plasmacytoma, light-chain (AL) amyloidosis, Hodgkin lymphoma, lymphoplasmacytic lymphoma, and essential thrombocythemia. Most of the patients responded to treatment with carbamazepine and had complete neurological resolution after specific treatment of the underlying neoplasms. Plasma exchange was also shown to improve neurological symptoms.

Conclusion

Paraneoplastic Isaacs syndrome is a rare neurological disorder that can present with muscle cramping, twitching, weakness, and sensory symptoms. This syndrome is diagnosed by specific EMG patterns defined as neuromyotonic and myokymic discharge. Patients usually respond to treatment with carbamazepine or phenytoin, and typically have complete neurologic resolution after specific treatment of neoplastic process.

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