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Anti-CASPR2-Antibody-Positive Isaacs' Syndrome Presenting with Myokymia, Neuropathic Pain, and Hyperhidrosis

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Dear Editor,

Isaacs' syndrome (IS) is an acquired autoimmune disorder and a peripheral nerve hyperexcitability syndrome characterized by muscle twitching, stiffness, and cramps.[1] Electromyography is used to diagnose IS based on the presence of myokymic and neuromyotonic discharges. Anti-voltage-gated potassium channel (VGKC)-complex antibodies, particularly the anti-contactin-associated protein-like-2 (CASPR2)-antibody (Ab), is associated with IS.[2] CASPR2-Ab inhibits interactions of CASPR2 and contactin-2, which might be the mechanism underlying IS.[3] Patients with CASPR2-Ab may develop IS in the presence of thymoma and myasthenia gravis (MG).[4] Here we report on a patient with CASPR2-Ab-positive IS who presented with tingling pain and hyperhidrosis as well as myokymia, highlighting various clinical features of IS and the mechanism of CASPR2-Ab.

A 57-year-old man presented with a 2-month history of muscle twitching, tingling pain, and dyspnea. He had been diagnosed with thymic carcinoma 14 years previously, at which time he was treated with thymectomy and radiotherapy. Lung metastasis had subsequently occurred twice, and was treated with resections. Multiple lung and pleural metastases had recurred and progressed despite treatment with imatinib, necessitating palliative radiotherapy (Fig. 1A). During radiotherapy, he developed fatigable ptosis. MG was diagnosed using repetitive nerve stimulation and positivity for anti-acetylcholine-receptor antibody. Prednisolone at 10 mg/day and azathioprine at 50 mg/day resulted in MG going into remission. Chest computed tomography performed 3 years later revealed an increased tumor burden, but the patient refused to undergo further treatment for thymic carcinoma. Six months later he developed muscle twitching and paresthesia in both limbs, hyperhidrosis, and dyspnea. A neurologic examination revealed intact mental status and cranial, motor, and sensory functions. Diffuse limb myokymia persisting during sleep was observed (Supplementary Video 1 in the online-only Data Supplement). The findings of motor and sensory nerve conduction studies were unremarkable. Electromyography revealed fasciculation potentials and myokymic discharges in the triceps and gastrocnemius (Fig. 1B). Laboratory tests showed nonspecific findings other than CASPR2-Ab in a fixed cell-based assay (Euroimmune, Luebeck, Germany) (Fig. 1C). Chest computed topography revealed progression of the tumor burden in the lungs and pleural metastasis, with invasion of the left hemidiaphragm and elevation of the right hemidiaphragm (Fig. 1D). Treatment with gabapentin and carbamazepine did not improve his myokymia or tingling pain. IS was diagnosed, and intravenous immunoglobulin therapy was started. This relieved the myokymia and tingling pain, but dyspnea worsened with hypercapnia. Due to the prolonged disease course, the patient refused to undergo invasive ventilation and died from respiratory acidosis.

This case highlights various clinical characteristics of IS. In addition to myokymia, the patient experienced severe tingling pain without numbness and with normal nerve conduction. The neuropathic pain of this case might be explained by persistent depolarization of the sen-

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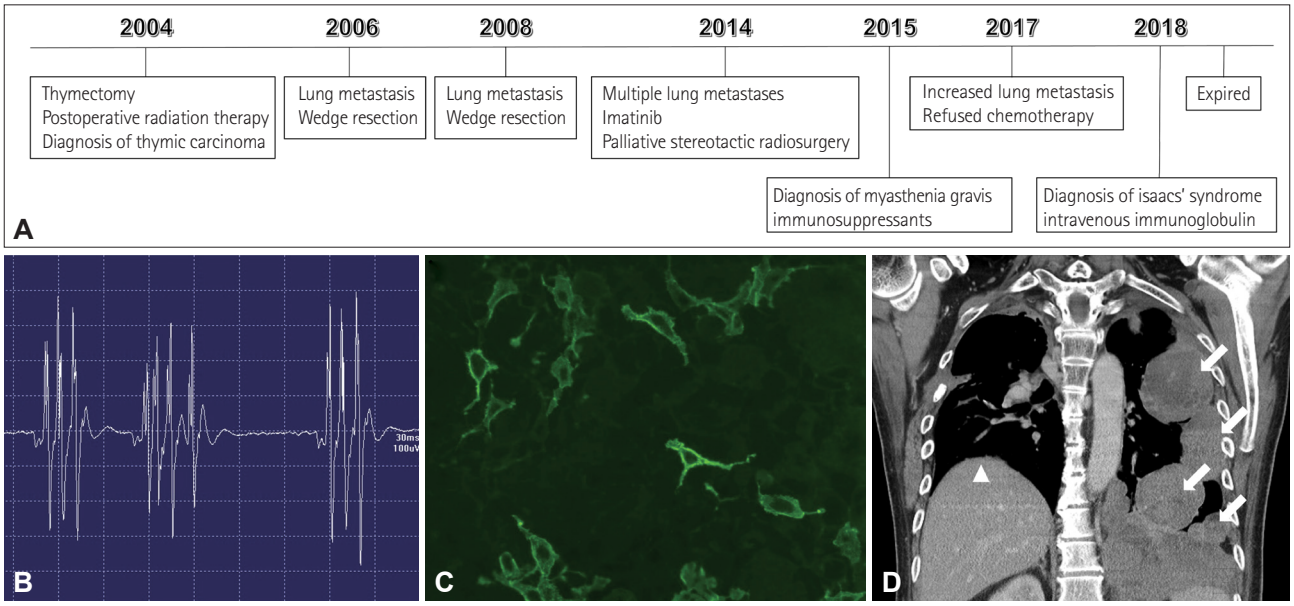

Fig. 1. Clinical course and laboratory findings in a case of Isaacs' syndrome. A: Clinical course of the case. B: Myokymic discharges in electromyography of the right triceps brachii muscle. C: Anti-contactin-associated protein-like-2 antibodies were detected in the cell-based assay of a plasma sample. D: Chest computed topography revealed progression of the tumor burden in the lungs and pleural metastasis, with invasion of the left hemidiaphragm (arrows) and elevation of the right hemidiaphragm (arrowhead).

sory nerves.[5] Microneurographic recordings demonstrating spontaneous activity of the sensory axons and in vitro dorsal-root ganglion-cell experiments showing repetitive firing support the concept of hyperexcitability of sensory nerves.[6,7] Hyperhidrosis is present in approximately half of these cases and is explained by direct autonomic involvement.[8] These findings suggest that CASPR2Abinduced hyperexcitability can affect the sensory and autonomic nerves as well as the motor nerves.

In summary, IS should be recognized clinically and diagnosed based on the findings of a CASPR2-Ab assay, particularly in the presence of MG and/or thymoma. Considering the mechanism of CASPR2-Ab-induced VGKC dysfunction in the peripheral motor, sensory, and autonomic nerves, clinical manifestations can vary from myokymia and neuropathic pain to dysautonomia. Intravenous immunoglobulin therapy, plasma exchange, and rituximab administration can be favorable treatment options for IS.

Supplementary Video Legend

Video 1. Intermittent muscle twitching in the right calf muscle.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.4.699.

Author Contributions

Conceptualization: Kwang-Kuk Kim. Data curation: Hyunjin Kim, Hye Weon Kim, Hyung Seok Ahn. Supervision: Young-Min Lim, Eun-Jae Lee, Kwang-Kuk Kim. Writing—original draft: Hyunjin Kim. Writing—review & editing: Young-Min Lim, Eun-Jae Lee, Hye Weon Kim, Hyung Seok Ahn, Kwang-Kuk Kim.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Ahmed A, Simmons Z. Isaacs syndrome: a review. *Muscle Nerve* 2015;52:5-12.
2. Lancaster E, Huijbers MG, Bar V, Boronat A, Wong A, Martinez-Hernandez E, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol* 2011;69:303-311.
3. Patterson KR, Dalmau J, Lancaster E. Mechanisms of Caspr2 antibodies in autoimmune encephalitis and neuromyotonia. *Ann Neurol* 2018;83:40-51.
4. Fleisher J, Richie M, Price R, Scherer S, Dalmau J, Lancaster E. Acquired neuromyotonia heralding recurrent thymoma in myasthenia gravis. *JAMA Neurol* 2013;70:1311-1314.
5. Rubio-Agusti I, Perez-Miralles F, Sevilla T, Muelas N, Chumillas MJ, Mayordomo F, et al. Peripheral nerve hyperexcitability: a clinical and immunologic study of 38 patients. *Neurology* 2011;76:172-178.
6. Shillito P, Molenaar PC, Vincent A, Leys K, Zheng W, van den Berg RJ,

et al. Acquired neuromyotonia: evidence for autoantibodies directed against K+ channels of peripheral nerves. *Ann Neurol* 1995;38:714-722.
7. Lance JW, Burke D, Pollard J. Hyperexcitability of motor and sensory neurons in neuromyotonia. *Ann Neurol* 1979;5:523-532.
8. Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002;125:1887-1895.