Isolated Autonomic Failure and Myoclonus as CASPR-2/VGKCs-antibodies paraneoplastic disorder in metastatic splenic relapse of advanced stage of malignant thymoma.

Fabrizia Terenghi[1], Chiara Gallo[1], Giuseppe Liberatore[1], Eduardo Nobile-Orazio[1-2]

Neuromuscular and Neuroimmunology Unit, Humanitas Clinical and Research Center – IRCCS, Via Manzoni 56, 20089 Rozzano – Milan, Italy

Department of Medical Biotechnology and Translational Medicine, Milan University, Milan, Italy

Isaac syndrome (IS) is a autoimmune or paraneoplastic condition, characterized by peripheral nerve hyperexcitability caused by voltage-gated potassium channel (VGKC)-complex antibodies.
Common manifestations: muscle twitching, stiffness, hypertrophy, weakness, dysautonomia (excessive sweating, weight loss)
IS is the second frequent paraneoplastic disease in thymoma patients.
Contactin-associated protein-like 2 (CASPR2) antibodies are mainly linked to peripheral nerve hyperexcitability, limbic encephalitis and neuropathic pain.
IS with paraneoplastic VGKC-complex autoantibodies associated showed clinical overlaps between patients with LGI1 and CASPR2 antibodies.

We report the case of a severe paraneoplastic dysautonomia, myoclonus and neuropathic pain in metastatic splenic relapse of thymoma with elevated serum CASPR-2 antibody in an advanced stage of disease.

A 50-year-old woman with a fifteen-year history of B3 stage IV metastatic thymoma, in the past she reported acute myositis-myasthenia gravis overlap syndrome during immunotherapy with PDL-1 and tyrosine-kinase inhibitors (TKI), without onconeural serum antibodies and successful treated with steroids.
She experienced first progressive radicular and neuropathic pain then episodes of orthostatic hypotension, sweating, and tachycardia associated with distal limbs myoclonus.

Neurological examination without muscle twitching, limb weakness or alterations in muscle. Myoclonus. Pain.

- ✓ MRI brain and lumbosacral: normal.
- Autonomic testing: severe symptomatic orthostatic hypotension and reduced cardiac variability suggestive of cardiovascular dysautonomia (impairment of the parasympathetic branch of the ANS).
- Nerve conduction studies and low- and high-frequency repetitive nerve stimulation: excluded peripheral neuropathy and pre/post-synaptic neuromuscular diseases. Spontaneous e continuous muscle fibre activity leading to neuromyotonia .
- ✓ Neuronal nicotinic acetylcholine receptors (α3/α7 nAChR) and LGI-1 antibodies: negative
  - CASPR-2 antibody: elevated titers
  - VGKCs antibody: slight increase
- ➢ Abdominal CT scan: splenic recurrence of disease

Treated with radiotherapy, resulting in initial clinical improvement of dysautonomic disturbances after administration of midodrine, ivabradine, and beta blockers.

Patients with CASPR2 antibodies could present CNS and PNS symptoms including neuromyotonia, Morvan syndrome, limbic or extensive encephalitis and neuropathic pain.
Autoimmune autonomic neuropathy usually occurs with AChR ganglionic (α3β4) antibody.
Our case revealed, in the thymoma contex, a predisposition to autoimmune disorders and a isolated CASPR2/VGKCs dysautonomic picture associated to hyperexcitability and pain, in metastatic splenic relapse of advanced stage of malignant thymoma.
IS should be recognized clinically and diagnosed based on the CASPR2 findings.
This antibodies target surface-exposed domains of or CASPR2 and appear to be directly pathogenic. In contrast, voltage-gated potassium channel (VGKC) antibodies that lack LGI1 or CASPR2 reactivities ('double-negative') are common in healthy controls and have no consistent associations with distinct syndromes.

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