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Letter to the Editor: New Observation

Paraneoplastic Anti-Neuronal Nuclear Antibody Type 3 Neurologic Autoimmunity

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Small-cell lung cancer (SCLC) is the most common malignancy associated with paraneoplastic neurologic syndromes (PNS).[1,2] In fact, PNS has been reported in approximately 9% of SCLC cases.[2] Furthermore, about half of the patients with PNS and an identifiable tumor have SCLC.[2] In 2001, Chan et al. described anti-neuronal nuclear antibody type 3 (ANNA-3), a very rare cause of PNS that is strongly associated with SCLC.[1] In this letter, we present a patient with paraneoplastic ANNA-3 neurologic autoimmunity leading to a diagnosis of SCLC.

A 71-year-old man with a 50-pack-year smoking history developed gradually progressive gait difficulty and paraparesis. He had a history of hypertension, dyslipidemia, usual interstitial pneumonia, and hearing impairment of unknown etiology. Over 6 months, he developed trouble walking on uneven ground. He had a 2-month history of progressive symmetric numbness in his hands and then his feet. One month after these symptoms started, he developed a dry cough, anorexia, and weight loss. He sought medical attention and had a computed tomography (CT) scan of the chest, abdomen, and pelvis to look for malignancy. The scan showed extensive lymphadenopathy in the mediastinum and right hilar region with a contiguous mass-like area in the right lower lobe, consistent with lung cancer. He subsequently had an endobronchial ultrasound and biopsy of lymph node station 4R. The cytology revealed small-cell carcinoma of lung origin. Staging magnetic resonance imaging (MRI) of the brain did not show evidence of intracranial metastases. Positron emission tomography was in keeping with limited-stage SCLC. Curative-intent chemoradiation was recommended to him but he decided to only proceed with combination carboplatin and etoposide chemotherapy. Carboplatin was chosen over cisplatin because of the hearing impairment and his new presumed sensory neuropathy.

He was assessed by a neuro-oncologist (SAC) a day after starting carboplatin chemotherapy. He had a spastic catch in the right arm, but normal tone elsewhere. The lower extremity power exam using the Medical Research Council scale was as follows: bilateral hip extension 4+, hip flexion 4, knee extension 4+, knee flexion 4, ankle plantar flexion 4+, and ankle dorsiflexion 4+. His reflexes were 2+ at all the deep tendon reflexes, except 1+ at the left ankle. He had an equivocal plantar response of the right foot and down-going plantar response of the left foot. He had stocking distribution pinprick loss. He had a normal vitamin B_{12} level, thyroid-stimulating hormone level, and hemoglobin A1C. There were no known toxic exposures. Montreal Cognitive Assessment to screen for limbic encephalitis was within normal limits. His MRI of the entire spine with gadolinium showed no abnormal enhancement or cord signal change. Electromyography and nerve conduction studies performed approximately 1 week after starting chemotherapy were in keeping with a predominantly sensory length-dependent axonal polyneuropathy. His motor amplitudes and velocities in the arm and leg were essentially normal. The sensory amplitudes and velocities were low, except for the ulnar amplitude (Table 1). Repetitive nerve stimulation studies (3 Hz) of the trapezius and nasalis showed no decrement. There was no facilitation of compound motor action potentials (CMAP) at either 1 or 3 minutes after exercise. Given these normal repetitive nerve stimulation studies and the normal CMAP amplitudes, Lambert–Eaton myasthenic syndrome was felt to be unlikely.

Serum neural antibody testing at the London Health Sciences Centre Clinical Immunology Laboratory detected ANNA-3/Dachshund-homolog 1 (DACH1)–immunoglobulin G (IgG) by mouse tissue indirect immunofluorescence (TIIF) (Fig. 1), which was confirmed by cell-based assay at the Mayo Clinic Neuroimmunology Laboratory. Lumbar puncture was not performed. The patient was started on an oral steroid pulse (prednisone 1,250 mg daily for 3 days) followed by a taper starting at 50 mg daily. Unfortunately, his function did not improve and he continued to use a walker for shorter distances and a wheelchair for longer distances. He died of COVID-19 approximately 3 months after beginning chemotherapy. He received only two cycles of combination carboplatin and etoposide. He never received treatment with an immune checkpoint inhibitor (ICI), a type of cancer immunotherapy used to treat extensive-stage SCLC.

In 2001, Chan et al. identified ANNA-3 in 11 of 68,000 patients with suspected PNS, based on characteristic immunofluorescence staining of mouse tissue sections.[1] Zekeridou *et al.* recently determined the ANNA-3 antigen to be DACH1 and reviewed the

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Table 1: The amplitudes and velocities of the sensory nerve conduction studies, accompanied by lab-specific normal values

Sensory nerve conduction studies				
Nerve	Amplitude (μV)	Normal amplitude (μV)	Velocity (m/s)	Normal velocity (m/s)
Median (Digit 3)	2.3	>10	39.9	>48
Ulnar	12.1	>12	38.7	>48
Radial	6.1	>10	46.6	>48
Sural	Not recordable	>5	Not recordable	>40
Superficial fibular	Not recordable	>5	Not recordable	>40

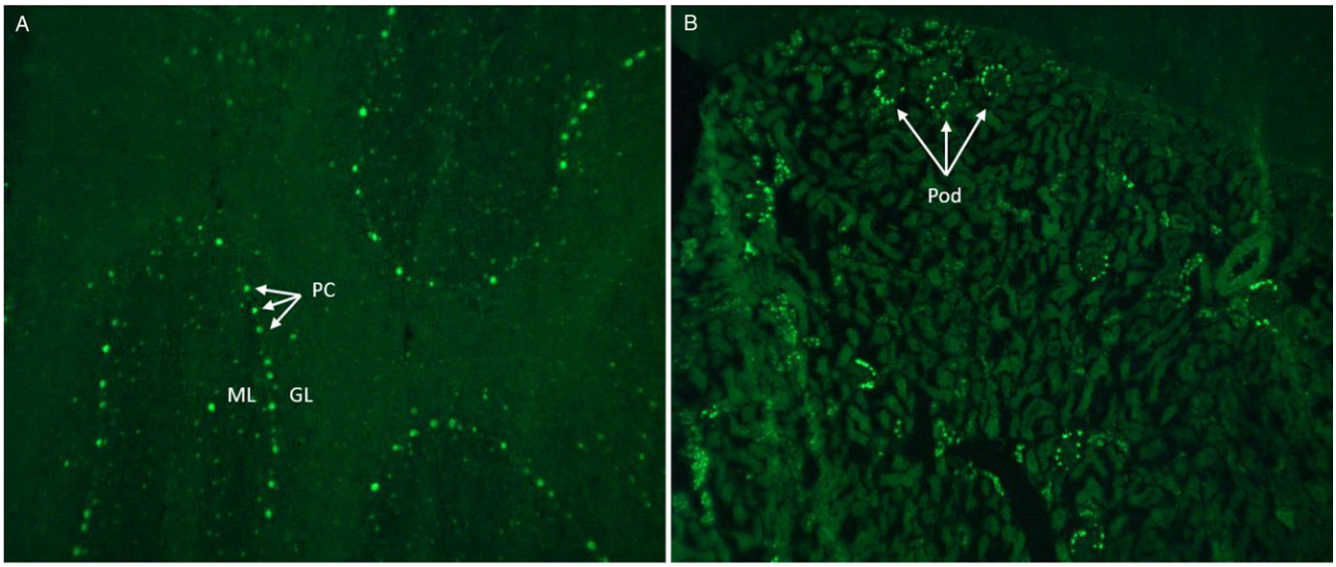

Figure 1: Detection of ANNA-3/DACH1-IgG by mouse TIIF. Mouse TIIF shows nuclear staining of Purkinje cells of the cerebellum (***a***) and glomerular podocytes of the kidney (***b***), compatible with ANNA-3/DACH1-IgG. GL = granular layer of the cerebellum; ML = molecular layer of the cerebellum; PC = Purkinje cells of the cerebellum; Pod = glomerular podocytes of the kidney.

available clinical information of 30 ANNA-3/DACH1-IgG-positive patients identified over a 28-year period.[3] Among them, 27 (90%) had evidence of malignancy. Nine of 22 patients with pathologically confirmed malignancy had SCLC and the remainder had other cancers (i.e., non-SCLC, neuroendocrine, colon, Merkel cell, breast, bladder, ovarian, and carcinoma of unknown primary), as well as ovarian teratoma. Detection of ANNA-3/DACH1 relies on TIIF, highlighting the importance of TIIF-based neural antibody testing for suspected central nervous system autoimmunity. The reported manifestations of ANNA-3/DACH1 neurologic autoimmunity are diverse, including sensory and sensorimotor neuropathies, cerebellar ataxia, myelopathy, dysautonomia, brainstem and limbic encephalitis, and stiff person syndrome.[1,3,4]

There are no studies to guide treatment specifically for patients with ANNA-3/DACH1 neurologic autoimmunity given its rarity. However, the treatment for PNS consists of treating the underlying malignancy and immunosuppressive therapies.[5] Eight of 11 patients with ANNA-3/DACH1 neurologic autoimmunity had improvement in their PNS with cancer and/or immunosuppressive treatment.[3] Two patients with SCLC were treated with ICI, which either exacerbated their ANNA-3 disease or made it appear.[3] In other case reports of patients with preexisting PNS, treatment with ICI therapy has been associated with a worsening of neurologic symptoms.[6,7,8] Given the limited data, we recommend caution and multidisciplinary management with neuro-oncology expertise if utilization of ICI therapy is being considered in these rare cases.

In summary, we have described a case of paraneoplastic ANNA-3 MRI-negative myeloneuropathy. Three examination findings pointed to myelopathy: (1) spastic catch, (2) preserved reflexes despite his neuropathy, and (3) equivocal right plantar response. Limitations of this case include only a few upper motor neuron findings, the lack of follow-up examination, the lack of follow-up imaging, and the potential for carboplatin toxicity contributing to his neuropathy.

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