CANOMAD Presenting as Bilateral Sixth Nerve Palsies

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A 67-year-old man reported 1 day of binocular horizontal diplopia associated with 1 week of bilateral periorbital pain, worse in the right eye. He felt otherwise well without any constitutional symptoms. Four days prior, he had undergone a partial right nephrectomy for grade II papillary renal cell carcinoma. Visual acuity was 20/20 in each eye, and the remainder of his ophthalmic examination was normal except for mildly limited abduction bilaterally, with a 16-prism diopter esotropia in primary gaze. Brain MRI, acetylcholine receptor antibodies, and thyroid-stimulating hormone level were normal.

Two weeks later, the patient had complete bilateral abduction deficits and was admitted to hospital. He was now found to have right upper and lower facial weakness, distal vibratory loss, and mild sensory ataxia. Deep tendon reflexes were absent at the biceps and brachioradialis, 1+ at the triceps, 2+ at knees, absent at the right ankle, and trace at the left ankle. Brain MRI was unremarkable. Lumbar puncture revealed an opening pressure 21 cm of H_2O, WBC 1/mL, RBC 1/mL, glucose 64 mg/dL, protein 98 mg/dL (normal: 15–45 mg/dL), and normal cytology. Serum protein electrophoresis was normal. Serum GQ1b antibodies were negative, and electromyography (EMG) study and nerve conduction study (NCS) were consistent with a sensory-predominant axonal polyneuropathy without demyelinating features. The patient was treated empirically for Miller Fisher syndrome with intravenous immune globulin (IVIg) 2g/kg. Despite treatment, he developed limited elevation of his left eye.

An extended ganglioside antibody panel was positive for asialo GM1, GM2, and GD1a antibodies. In light of these results and the chronicity of his clinical course, the patient was diagnosed with CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, M-protein agglutination, and disialosyl antibodies) and was treated with monthly IVIg, oral prednisone, and later rituximab. Ocular motility improved, although at 1 year of follow-up, he continued to have a residual 25-prism diopter esotropia for which he underwent successful strabismus surgery.

First described in 1985, CANOMAD is a rare, chronic, often relapsing autoimmune polyneuropathy characterized by sensory ataxia, areflexia, and prominent ophthalmoparesis (1). Sensory ataxia can be quite severe in CANOMAD and may result in loss of ambulatory function, but limb strength is generally spared. Antibodies against multiple disialosyl-containing gangliosides include GD1a, GD1b, GT1b, GD2, GD3, GM3, and GQ1b (2). These antibodies often are reflected as an IgM paraprotein on serum protein electrophoresis and may act as cold agglutinins in 50% of patients. The etiology of these antibodies is unknown; cross-reactivity with bacterial lipopolysaccharides has been suggested as a potential mechanism, although our patient lacked a history of antecedent infection. Electrophysiologic studies (EMG and NCS) typically demonstrate an axonal sensorimotor polyneuropathy; demyelinating features may also be present. Cerebrospinal fluid (CSF) examination occasionally reveals albuminocytologic dissociation, as in our patient, but in most patients, the CSF protein level is normal. Peripheral nerve biopsies reveal variable demyelination and axonal loss (2,3). Brain imaging is unremarkable.

Ophthalmoparesis is usually the initial manifestation of CANOMAD but may rarely be delayed or absent. In one large case series, 16 of 18 patients had ophthalmoparesis due to third, fourth, or sixth cranial neuropathies, and some had trigeminal and facial nerve involvement (2). In another series of 11 patients with polyneuropathy and anti-GD1a antibodies, 10 were found to have neuro-ophthalmic abnormalities described as limited abduction, nystagmus, ptosis, limited eyelid closure, nonreactive pupils, limited upgaze, impaired saccadic eye movements, and bifacial weakness (3). One study reported a pseudodorsal midbrain syndrome that included pupillary light-near dissociation and convergence-retraction nystagmus (4). There are isolated reports of patients with progressive optic neuropathy in CANOMAD as well (5).

CANOMAD likely exists on a similar pathophysiologic spectrum as Miller Fisher syndrome. The key distinction between these 2 entities lies in the onset and temporal course of the disease. In Miller Fisher syndrome, symptoms typically peak after 1 week, plateau for 2 weeks, and resolve by 3 months (9), whereas CANOMAD progresses over a period of months and can often extend over decades punctuated by relapses. Serum GQ1b antibodies are present in over 80% of patients with Miller Fisher syndrome (6). Although the lack of paraprotein or cold agglutination limits a definite diagnosis in our patient, the absence of GQ1b antibodies and prolonged temporal course suggested a likely diagnosis of CANOMAD rather than Miller Fisher syndrome.

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There are no previously published associations between CANOMAD and malignancy or recent surgery, as were found in our patient. There are rare paraneoplastic neuropathies associated with antiganglioside antibodies in diffuse large B-cell lymphoma and chronic lymphocytic leukemia, but these lack ophthalmoparesis and more closely resemble chronic inflammatory demyelinating polyneuropathy. Paraneoplastic neurologic syndromes are uncommon in renal cell carcinoma, and our patient did not develop any brainstem or cerebellar signs to suggest a paraneoplastic brainstem encephalitis or cerebellar degeneration.

A limited number of studies have addressed the management of patients with CANOMAD. Favorable results have been reported with both IVIg (7) and rituximab (8). Our patient improved with both treatments and has had no further relapses. He had a residual esotropia that was corrected with strabismus surgery and has, thus far, not recurred.

STATEMENT OF AUTHORSHIP

Category 1: a. conception and design: A. G. Hamedani and M. A. Tamhankar; b. acquisition of data: A. G. Hamedani and M. A. Tamhankar; c. analysis and interpretation of data: N/A. Category 2: a. drafting the manuscript: A. G. Hamedani; b. revising it for intellectual content: A. G. Hamedani, S. J. Bird, and M. A. Tamhankar. Category 3: a. final approval of the completed manuscript: A. G. Hamedani, S. J. Bird, and M. A. Tamhankar.

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