Paraneoplastic autoimmune neurological disorders are a remote manifestation of a patient’s immune response initiated by onconeural antigens expressed in a cancer that is often occult. Paraneoplastic autoantibody detection aids the neurological diagnosis and generally predicts a limited number of potentially associated cancer types but not a specific neurological presentation. Antibodies reactive with plasmalemmal channels and receptors have the potential to cause the neurological dysfunction, while antibodies reactive with neural nuclear and cytoplasmic autoantigens are surrogate markers for cytotoxic T cells specific for peptides derived from intracellular autoantigens. The difficulty with imaging cancers in the context of neurological autoimmunity attests to the efficacy of the antitumor response. In a minority of cases, no cancer is found.

Neuromyelitis optica (NMO) is a severe relapsing autoimmune inflammatory demyelinating disease that preferentially affects the optic nerves and spinal cord, thus mimicking multiple sclerosis, from which it is distinguished by a serum autoantibody specific for the astrocytic water channel, aquaporin-4 (AQP4). There is compelling evidence that AQP4 IgG is pathogenic in NMO. Neuritis optica (NMO) spectrum disorders (NMOSDs, unified by AQP4-IgG seropositivity) have been reported in a paraneoplastic context. In 2 cases, AQP4 was found in the tumor tissue. Here we describe a patient with a small-bowel neuroendocrine tumor who presented with NMOSD. The serum test result was positive for AQP4 IgG, and metastatic cells in the patient’s liver expressed AQP4 immunoreactivity.

### Report of a Case

A 48-year-old woman with a history of sticky platelet syndrome, antiphospholipid syndrome, and increased von Willebrand factor activity had multiple episodes of deep venous thrombosis and a pulmonary embolus more than 5 years prior to her first neurological symptoms. Ten months before coming to our attention, she presented elsewhere with painless left-sided partial vision loss of sudden onset, which was diagnosed as a stroke; 3 months later, she experienced more than 2 days’ decreased sensation and paresthesias involving the entire right leg. Examination revealed reduced pinprick and light touch perception in that leg; motor function and reflexes were normal. The findings from head magnetic resonance imaging (MRI), magnetic resonance angiography of the head and neck, echocardiogram, and routine cerebrospinal fluid studies were normal. Five months later, findings from cervical and thoracic spine MRI, without and with gadolinium infusion, were normal. Vision assessment noted acuity limited to hand motion, pale discs, sluggish pupillary response to light, and left afferent pupillary defect. The remaining neurological examination findings were normal apart from mild residual sensory changes and brisk patellar reflexes. She presented to the Neurology Department at Wayne State University with bilateral leg weakness, ascending paresthesias, and decreased sensation.
signs of systemic lupus erythematosus or Sjögren syndrome. Examination revealed severe paraparesis and a sensory level at T10.

Spine MRIs showed continuous T2 hyperintensity (C6 to T4 at the time of maximum illness), with focal patchy gadolinium enhancement and cord swelling at T3-T4 (Figure 1). Brain MRI findings were normal. Cerebrospinal fluid was acellular with normal total protein, IgG index was 0.60 (normal), and there were no supernumerary oligoclonal bands (5 noted in serum). Positive serology results included antinuclear antibody (1:160, mixed speckled and homogeneous pattern), double-stranded DNA (1:80), and Smith antibody (25.1; normal, <25.0), as well as persistent lupus anticoagulant and AQP4 IgG (enzyme-linked immunosorbent assay, >160 units; normal, <5 units/mL; positive AQP4-transfected cell-binding assay). The results of a comprehensive paraneoplastic antibody panel were positive for muscle acetylcholine receptor antibodies (2.3 nmol/L, normal <0.02 nmol/L) but were negative for other paraneoplastic antibodies including antineuronal nuclear antibody-1, amphiphysin IgG, and collapsin response-mediator protein 5 IgG, which are antibodies associated with myelopathies. Antimuscle acetylcholine receptor is encountered in 11% of AQP4-IgG-positive NMO serum samples and 2% of patients with NMO have myasthenia gravis.10 High-dose intravenous prednisolone therapy was followed by plasma exchange.

Anemia was noted at hospital admission and abdominal pain, hematemesis, and diarrhea developed. Her history included resection of a small-bowel neuroendocrine tumor 6 years earlier (no follow-up). An abdominal computed tomographic scan revealed several hepatic hypervascular masses. Biopsy confirmed metastatic carcinoid. Hematoxylin and eosin and immunohistochemical (anti-AQP4 antibody incubated at 4°C overnight, Sigma-Aldrich, AS971, dilution 1:250; no antigen retrieval) stainings of formalin-fixed paraffin embedded sections (5 μm) revealed AQP4-positive tumor cells (reddish cytoplasm) scattered within nests of nonimmunoreactive tumor cells (Figure 2). Octreotide acetate therapy was started, right hepatic artery radioembolization was performed, and rituximab was infused every 6 months. The patient had no further episodes of leg weakness, is able to ambulate without assistance (25-foot walk), and has no progression of her liver metastasis 30 months after her initial presentation.

Wayne State University institutional review board approval was waived and written informed consent was obtained from the patient.

Discussion

The demonstration of AQP4 immunoreactivity in this patient’s tumor further supports a paraneoplastic etiology for some NMOSD cases. Breast carcinoma is the most common neoplasm reported with paraneoplastic NMOSD, but a previous case of carcinoid has been reported.6 Carcinomas of the lung, uterus, thymus, cervix, bladder, and thyroid; seminoma; ovarian teratoma; pituitary adenoma; lymphoma; and monoclonal gammopathy also have been reported.6-9 Aquaporin-4 is expressed normally in a variety of noncentral ner-
Figure 2. Aquaporin-4 Immunoreactivity in Carcinoid Tumor Cells

A. There is a sharp border between the hypercellular tumor (lower left) and normal liver parenchyma (upper right; hematoxylin and eosin).
B. Tumor cells are shaped irregularly with hyperchromatic nuclei and pink cytoplasm (hematoxylin and eosin).
C. Aquaporin-4–positive tumor cells (reddish cytoplasm) are relatively sparse and scattered within nests of nonimmunoreactive tumor cells (arrowheads). D. Aquaporin-4 immunoreactivity appears to be predominately cytoplasmic (arrowheads). Scale bars indicate 100 μm (A), 20 μm (B and C), and 10 μm (D).

It is noteworthy that 2 other paraneoplastic autoimmune mimics of multiple sclerosis exhibit symmetric, longitudinally extensive tract changes resembling signal abnormalities characteristic of spinal cord MRIs typical of NMOSD lesions: relapsing optic neuropathy and myelopathy associated with collapsin response-mediator protein 5 IgG (usually associated with small-cell carcinoma) and myelopathy associated with amphiphysin IgG (with breast or lung carcinoma).

The median onset age for idiopathic NMO is 39 years, but patients with paraneoplastic NMO generally present at older than age 55 years. Recent reports indicate that 12% to 16% of patients with NMOSD are older than age 50 years at initial diagnosis. Generally, one considers a paraneoplastic disorder in those older than 55 years of age but, with respect to NMO recommendations, await more investigations.
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