Objective: To investigate the full extent of Purkinje cell cytoplasmic autoantibody type 1 autoimmunity (classically associated with paraneoplastic cerebellar degeneration) from clinical, immunohistochemical, and neuropathological perspectives.

Design: Case series.

Setting: Mayo Clinics, 3 sites (Minnesota, Arizona, and Florida).

Patients: Of 133,138 patients tested over a 21-year period, 83 (0.06%) were identified as seropositive for Purkinje cell cytoplasmic autoantibody type 1 IgG.

Main Outcome Measures: The frequency of cerebellar and noncerebellar disorders and the clinical outcomes (neurological and oncological) of the patients.

Results: All patients were women. At initial presentation, 64 patients (77%) had a cerebellar disorder, and 19 patients (23%) had an extracerebellar disorder. Over the clinical course, neurological symptoms and signs were multifocal in 50 patients (60%), and they involved the cerebellum (89% of patients), the pyramidal tract (30%), the brainstem (13%), and the spinal anterior horn cells or peripheral nerve (10%; frequently upper limb predominant); 11% of patients did not develop cerebellar ataxia. Serological and neuropathological findings were observed in the cerebellum, the brainstem, the spinal cord, the anterior horn, and the dorsal root ganglion that paralleled the diversity of clinical signs. After a median follow-up of 18 months, 1 or more carcinomas had been detected in 88% of patients: ovarian epithelial cancer (53%), breast cancer (22%), fallopian tubal cancer (11%), primary peritoneal cancer (5%), metastases of unknown primary cancer (4%), and other cancers (4%). Sustained improvement was reported in 15% of patients following oncological or immunological therapies. Voltage-gated calcium channel antibodies coexisted in 23 patients (28%).

Conclusions: Purkinje cell cytoplasmic autoantibody type 1 autoimmunity most commonly affects the cerebellum, but the spectrum of neurological symptoms and presentations is broad. Neurological outcomes are usually poor, even when cancer remission is achieved.

METHODS

The study was approved by the institutional review board of Mayo Clinic in Rochester, Minnesota (IRB no. 2619-04). In a 21-year period (1987-2007), the Mayo Clinic Neuroimmunology Laboratory performed prospective indirect immunofluorescence-based screening of serum samples and cerebrospinal fluid (CSF) samples from 133,138 patients seen at Mayo Clinic’s 3 sites: Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida. Purkinje cell cytoplasmic autoantibody type 1 IgG was detected in 83 patients (0.06%). Data on the demographic and clinical characteristics of each patient were obtained from a review of the clinical records. Additional information regarding cause of death was obtained by a review of the medical records and death certificate data, when available. We used a previously described and clinically validated indirect immunofluorescence assay to detect PCA-1 IgG.9 Neuropathologic data were obtained from 2 autopsied patients. The relationship between serum and CSF PCA-1 IgG titers in individuals for whom both serum and CSF samples were available was evaluated using the coefficient of determination ($R^2$), by use of JMP version 8.0 (SAS Institute Inc, Cary, North Carolina).

RESULTS

PATIENTS’ DEMOGRAPHICS

Of 133,138 patients tested over a 21-year period, 83 (0.06%) were identified as seropositive for PCA-1 IgG (mean number of patients per year was 4). All were women. Median age at neurological symptom onset was 60 years (range, 31-80 years). With regard to race/ethnicity, 77 patients (93%) were white, 3 patients (4%) were Native American, 1 patient (1%) was African American, 1 patient (1%) was Asian, and 1 patient (1%) was of unknown race/ethnicity. Follow-up information was available for 74 patients (median follow-up period, 18 months [range, 1-204 months]).

INITIAL NEUROLOGICAL MANIFESTATIONS

Neurological presentations were subacute in all patients and multifocal in 50 patients (60%). Cerebellar ataxia was the predominant presentation in 64 patients (77%). Nineteen patients (23%) initially presented with 1 or more of the following: a brainstem disorder (eye movement disorders [5 patients], hyperacusis [1 patient], vertigo [1 patient], pseudobulbar palsy [1 patient], intractable vomiting [1 patient], and bilateral trigeminal neuropathies [1 patient]); peripheral neuropathy (8 patients); myelopathy (4 patients); and subacute cognitive decline (1 patient). Within a median interval of 2 months (range, 1-12 months), 10 of these 19 patients (53%) ultimately manifested signs of cerebellar ataxia.

SPECTRUM OF NEUROLOGICAL MANIFESTATIONS

Central Nervous System Disorders

Cerebellar ataxia developed in 74 patients (89%) and was ultimately the most disabling problem. Twenty-five patients (30%) manifested signs of corticospinal tract dysfunction: 13 had a Babinski sign, 10 had ataxic-spastic dystartria, 9 had spasticity, and 2 had pure spastic dystartria. Brainstem abnormalities or cranial neuropathies, recorded in 11 patients (13%), included supranuclear gaze palsy (3 patients), unilateral sixth nerve palsy (2 patients), bilateral sixth nerve palsies (2 patients), fourth nerve and bilateral seventh nerve palsies (1 patient), ocular bobbing (1 patient), bilateral trigeminal neuropathies (1 patient), and unilateral ptosis (1 patient). Other documented neurological findings of recent onset included cognitive impairment or personality change (4 patients [5%]), dystonia (2 patients [2%]), and rest tremor (2 patients [2%]).

Peripheral Neuropathy

Eight patients (10%) had a somatic peripheral neuropathy or lower motor neuronopathy not attributable to alternative causes, all at initial presentation (Table 1). These findings coincided with cerebellar symptom onset in 4 patients, preceded cerebellar symptom onset in 2 patients, and were the exclusive neurological manifestation in 2 patients. Clinical presentations were weakness and numbness of upper and lower extremities (2 patients), weakness and sensory loss in upper extremities (2 patients), progressive upper and lower extremity weakness (1 patient), progressive upper and lower extremity weakness with leg paresthesias (1 patient), bilateral upper extremity and facial sensory loss (1 patient), and bilateral upper and lower extremity sensory symptoms (1 patient). A remarkable feature of the extremity symptoms was the initial or predominant involvement of upper limbs in 4 of the 8 patients.

Dysautonomia

Focal dysautonomia (gastrointestinal dysmotility) was reported in 2 patients: one with pseudo-obstruction of the small bowel and the other with gastroparesis. Both patients also had cerebellar ataxia.

NEURAXIS IMAGING

The following abnormalities were noted in 35 of the 75 patients (47%) for whom brain neuroimaging data were available: isolated cerebellar atrophy (25 patients), generalized cerebral and cerebellar atrophy (7 patients), pontine atrophy (1 patient), diffuse T2-weighted signal abnormalities in the brainstem (1 patient), and trigeminal nerve enhancement (1 patient). Magnetic resonance imaging of the spinal cord revealed diffuse abnormal T2-weighted signal of the spinal cord in 1 patient (patient 7 [Figure 1 and Table 1]).

FINDINGS FROM IMMUNOFLUORESCENCE AND WESTERN BLOT ASSAYS

Purkinje cell cytoplasmic autoantibody type 1 IgG was detected in the serum samples of 81 patients (98%) and in the CSF samples of 18 patients (22%); of the 18 patients whose CSF samples were positive for PCA-1 IgG, 2 (11%) had serum samples that tested negative for PCA-1 IgG. Purkinje cell cytoplasmic autoantibody type 1 positivity was
confirmed in all cases by use of a native Western blot assay with a water-soluble antigen preparation extracted from the cerebellar cortex of an adult rat. 10 When both the serum and CSF samples tested positive for PCA-1 IgG, serum titers ranged from 480 to 983 040 (median, 15 360; normal range, <120), and CSF titers ranged from 128 to 32 768 (median, 512). The serum titer moderately predicted the CSF titer in those patients (R²=0.466). Titers for the 2 patients for whom only CSF samples yielded a positive result were 32 and 16, respectively. All serum samples fulfilled established immunohistochemical criteria for PCA-1 IgG and also bound to cytoplasmic elements in hippocam-
pal neurons, spinal cord neurons, the dorsal root ganglion, the nerve root (Figure 2), and Schwann cells in peripheral nerve, as reported previously.7

NEUROPATHOLOGICAL FINDINGS

The neural tissues of 2 autopsied patients (patients 9 and 10) were evaluated histopathologically. When these 2 patients were alive, they both had clinical signs of mixed cerebellar and pyramidal tract impairment. The cerebellum, brainstem, spinal cord (at all levels), and dorsal root ganglia exhibited widespread perivascular inflammation, microglial activation, microglial nodules, patchy neuronal loss, and gliosis (Figure 3). Immunophenotyping of lymphocytes revealed a predominance of peripheral and parenchymal CD8⁺ T cells. The results of gross and microscopic examinations of the cerebral hemispheres were normal in both patients. The interval from symptom onset to autopsy was 17 months for patient 9 and 4 months for patient 10.

ONCOLOGICAL ASSOCIATIONS

Cancer was detected in 73 patients (88%) and was a Mullerian or breast carcinoma in 69 of the 73 patients (95%) (Table 2). In 67 of the 73 patients (92%), the cancer was limited to 1 anatomical site, and in 6 of the 73 patients (8%), it was locally invasive or had limited regional metastases. One patient had a recurrent ovarian carcinoma. Two patients had multiple, newly diagnosed malignant neoplasms (ovarian epithelial and fallopian tubal carcinomas [1 patient] and breast and primary peritoneal carcinomas [1 patient]), and 9 patients had a past history of cancer without evidence of recurrence (breast carcinoma [6 patients], colon carcinoma [1 patient], lymphoma [1 patient], and primary eyelid adenocarcinoma [1 patient]). Three of the 4 patients whose newly detected cancer was not a Mullerian or breast carcinoma had an adenocarcinoma metastasis from an unidentified primary source, and the fourth patient had lymphoma.

When a primary or metastatic cancer was not initially identified by routine imaging (ultrasonography or computed tomography), direct visualization during laparotomy (4 patients) or laparoscopy (1 patient) identified the primary site of cancer (ovary [4 patients] and fallopian tube [1 patient]). For 4 patients with primary peritoneal adenocarcinoma, the tumor was initially identified by use of computed tomography (demonstrating peritoneal caking or studding in 2 patients), during clinical presentation with cecal obstruction and subsequently by use of laparotomy (1 patient), and by use of ascitic fluid cytology (1 patient).

The median duration of cancer surveillance was shorter for the 10 patients in whom no cancer was found (11 months; range, 1-31 months) than for patients in whom cancer was found (22 months; range, 1-204 months). In 40 of the 83 patients (48%), the neurological disorder preceded cancer diagnosis. Detection of PCA-1 IgG preceded the diagnosis of cancer in 37 patients (45%).

OTHER CSF ABNORMALITIES

The CSF samples of 50 patients were analyzed; abnormalities were found in the samples of 38 of the 50 patients (76%). The findings are summarized in Table 3.

TREATMENT AND OUTCOMES

Information regarding treatment and outcomes was available for 67 patients (11 previously reported).11 The treating physicians reported sustained neurological stabilization or mild improvement in 10 of the 67 patients (15%): 5 patients received both chemotherapy and immunotherapy (cyclophosphamide [3 patients], plasma exchange [3 patients], corticosteroids [3 patients], and intravenous immune globulin [1 patient]); 3 patients received chemotherapy alone; and 2 patients received immunotherapy alone (intravenous immune globulin and steroids [1 patient] and plasma exchange and steroids [1 patient]). Neurological improvements following chemotherapy or immunotherapy were mild and transient in 14 other patients (17%). Neurological improvements did not correlate significantly with duration of symptoms prior to treatment or with cancer type. Death was reported in 40 patients (median survival from onset of neurological symptoms was 24 months [range, 1-204 months]); 6 of 67 patients (9%) survived for at least 5 years. Information regarding the cause of death was available for 11 patients (respiratory failure complicating a paraneoplastic neurological disorder [7 patients], metastatic cancer [3 patients], and ischemic stroke [1 patient]).

COMMENT

Because the patients in our study were ascertained sequentially in the course of comprehensive paraneoplastic serological evaluation (rather than being patients with ataxia only), the authors were able to determine the breadth of accompanying neurological disorders. Although most
patients presented with cerebellar ataxia, 89% ultimately developed ataxia, 23% had other neurological problems at onset, and 11% had only noncerebellar disorders. Neurologists commonly reserve serological testing for PCA-1 IgG for female patients presenting with isolated cerebellar ataxia, but our observations justify consideration of a PCA-1 IgG–related neurological disorder in adult female patients presenting with neurological symptoms of subacute onset without evidence of ataxia. All patients in this series were women. Of the 332 non–Mayo Clinic patients whom we identified in the same period and who were positive for PCA-1 IgG, 6 (2%) were men.
A broader phenotype beyond cerebellar ataxia has been reported previously but either in case reports or in a large series in which all patients had cerebellar ataxia in addition to other findings. Descriptions previously reported have included brainstem disorders and myelopathy, peripheral neuropathy, motor neuronopathy, gastrointestinal dysmotility, cognitive impairment, downbeat nystagmus, and chorea occurring in the setting of PCA-1 IgG. One patient was reported to have normal cognition and fluctuating mesial temporal lobe abnormalities determined by use of magnetic resonance imaging. In contrast to our own series, 2 large series have reported ataxia to be present in all patients positive for PCA-1 IgG. In one series of 55 patients, coexisting neurological disorders were described as common but usually mild; and in the other series, all 50 patients were described as having an isolated pancerebellar syndrome.

Consistent with previous neuropathological reports, autopsied cerebral nervous system tissue from 2 patients in our study revealed multifocal inflammatory changes, with perivascular and parenchymal CD8+ cytotoxic T lymphocytes throughout the cerebellum, brainstem, spinal cord, and nerve rootlets. The occurrence of the patients’ clinical, radiological, and pathological findings in these regions is consistent with published data indicating cdr2 in neocortical and brainstem neurons, in addition to the cerebellum, and the distribution of cdr2 proteins in mouse tissues, which was revealed in our study by PCA-1 IgG immunoreactivity (in the dorsal root ganglia, enteric nervous system, large neurons in the hippocampus and brainstem, and Schwann cells of the peripheral nervous system). This does not imply that PCA-1 IgG is pathogenic in vivo, but it does reveal the distribution of the neural protein from which antigenic peptides are derived for surface display on major histocompatibility complex class I proteins upregulated by proinflammatory cytokines.

Consistent with early reports, the predominant oncological associations were mullerian and breast carcinomas, and exploratory surgery was frequently required to detect a mullerian malignant neoplasm prior to histologi-
multiply by 10.0; and to convert WBC count to

cal diagnosis.21 No patient had endometrial carcinoma, which is another documented oncological association of PCA-1. One patient is still alive 19 years after the onset of neurological symptoms. In contrast to the experience that we report here (and in contrast to our clinical experience of non-Mayo Clinic patients), an earlier publication reported death due to metastatic carcinoma in 12 of 23 patients positive for PCA-1 IgG (52%).22

Although PCA-1 IgG serves as a marker of paraneoplastic neurological disorders related to breast and müllerian carcinoma, the most cogent evidence points to the antibody not being pathogenic.31 The target antigen of PCA-1, cdr2, is a cytoplasmic antigen and therefore unlikely to be accessible to a circulating antibody. Data from Albert et al5 support a neural peptide-specific T cell-mediated attack on neurons as the basis of irreversible neurological impairment in patients positive for PCA-1 IgG. Albert et al5 demonstrated that antigen-specific cytotoxic T cells were activated in vitro by major histocompatibility complex–matched dendritic cells presenting cdr2 peptides to circulating T cells isolated from seropositive patients. Emigration from tumor-draining lymph nodes to the systemic circulation and thence to the central nervous system of expanded populations of major histocompatibility complex class I–restricted, CD8+ onconeural peptide-specific cytotoxic T lymphocytes is a plausible mechanism for selective neuronal degeneration in patients with PCA-1 autoimmunity.

Table 2. Data on 84 Malignant Neoplasms Identified in 73 Patients Positive for Purkinje Cell Cytoplasmic Autoantibody Type 1 IgG

<table>
<thead>
<tr>
<th>Anatomical Site</th>
<th>Histological Type</th>
<th>Patients, No. (%) (n=73)</th>
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<tbody>
<tr>
<td>Ovary</td>
<td>Adenocarcinoma</td>
<td>45 (62)</td>
</tr>
<tr>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Adenocarcinoma</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Serous surface</td>
<td>Papillary (primary peritoneal adenocarcinoma)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Metastatic adenocarcinoma</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymphoma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Colon</td>
<td>Adenocarcinomaa</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Upper eyelid</td>
<td>Adenocarcinomaa</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

aCancer was detected in 73 seropositive patients (88%).
bCoexisting müllerian or breast carcinoma.

<table>
<thead>
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<th>Table 3. Data on Cerebrospinal Fluid Samples</th>
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<tr>
<td>CSF Parameter</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Total protein serum level, mg/dL</td>
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<tr>
<td>WBC count, cells/mL</td>
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<tr>
<td>IgG index</td>
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<td>Oligoclonal bands, No.</td>
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Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.

Statistical analysis: r2 test was used to compare rates of PCA-1 IgG between patients with serous surface and patients without serous surface, with a P-value of less than 0.05 set as the statistical threshold for significance.

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Financial Disclosure: Dr Lennon and the Mayo Clinic have a financial interest in the intellectual property entitled “NMO-IgG: A Marker Autoantibody of Neuromyelitis Optica.” A patent has been issued for this technology, and it has been licensed to commercial entities. Drs Lennon and Pittock have a potential financial interest in the technology entitled “Aquaporin-4 Antigen as a Cancer Marker.” A nonprovisional patent application has been filed by Mayo Clinic for this technology, and it has been licensed by Mayo Clinic to a commercial entity. No royalties have accrued from this license. Drs Lennon and Pittock have a potential financial interest in the technology entitled “Aquaporin-4 Binding Autoantibodies in Patients with Neuromyelitis Optica Impair Glutamate Transport by Down-Regulating EAAT2.” A nonprovisional patent application has been filed by Mayo Clinic for this technology.

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