Neuro-Ophthalmologic Manifestations of Paraneoplastic Syndromes

Melissa W. Ko, MD, Josep Dalmau, MD, PhD, and Steven L. Galetta, MD

Abstract: Paraneoplastic syndromes with neuro-ophtalmologic manifestations may involve the central nervous system, cranial nerves, neuromuscular junction, optic nerve, uvea, or retina. Most of these disorders are related to immunologic mechanisms presumably triggered by the neoplastic expression of neuronal proteins. Accurate recognition is essential to appropriate management.

PARANEOPLASTIC CEREBELLAR DEGENERATION

Paraneoplastic cerebellar degeneration (PCD) is a syndrome of subacute severe pancerebellar dysfunction (Table 1). Initially, patients present with gait instability. Over several days to weeks, they develop truncal and limb ataxia, dysarthria, and dysphagia. The cerebellar disease eventually stabilizes but leaves patients incapacitated.

PCD is most commonly associated with cancers of the lung, ovary, and breast and with Hodgkin disease (7). Ocular motor manifestations include nystagmus, ocular dysmetria, saccadic pursuit, saccadic intrusions and oscillations, and skew deviation (8). Over the last 30 years, at least nine anti-neuronal antibodies have been associated with PCD. However, only about 50% of patients with suspected PCD test positive for anti-neuronal antibodies in serum or cerebrospinal fluid (CSF) (9). Anti-Yo and anti-Tr are the autoantibodies most commonly associated with a pure paraneoplastic cerebellar syndrome (Table 2). PCD is pathologically characterized by severe, diffuse cerebellar Purkinje cell loss with proliferation of Bergmann glia and sometimes infiltrates of inflammatory cells in the deep cerebellar nuclei.

PCD associated with anti-Yo is usually found in postmenopausal women with breast or ovarian cancer presenting at approximately 60 years of age. Peterson et al (10) reported that of 55 patients positive for anti-Yo antibody, all had findings of horizontal nystagmus (Table 3). Some had downbeat nystagmus with an additional rotatory or vertical component. Diplopia was present in approximately one third of these patients. Rare neuro-ophtalmologic findings included opsinclonus and progressive visual loss. Cohen et al (11) reported a patient with anti-Yo PCD who had recurrent anterior uveitis, upward gaze palsy with eyelid retraction, bilateral sixth cranial nerve palsies, and skew deviation. The initial search for a malignancy was negative. However, an update to the case reported 5 years later indicated that a poorly differentiated carcinoma, probably of breast origin, in a right axillary lymph node was found on positron emission tomography (PET) and confirmed by biopsy. This carcinoma had strong expression of Yo antigen (12). Prognosis in anti-Yo PCD is generally
Paraneoplastic Syndromes


TABLE 1. Paraneoplastic syndromes of neuro-ophthalmologic significance

<table>
<thead>
<tr>
<th>Paraneoplastic encephalitides</th>
<th>Brain stem</th>
<th>Encephalomyelitis</th>
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<tbody>
<tr>
<td>Anti-Ma2 encephalitis</td>
<td>Anti-NMDA receptor encephalitis</td>
<td></td>
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<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Opsoclonus-myoclonus</td>
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<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>Paraneoplastic stiff-person syndrome</td>
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<tr>
<td>Paraneoplastic syndromes of retina and optic nerves</td>
<td>Paraneoplastic retinopathies</td>
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<tr>
<td>Cancer-associated retinopathy</td>
<td>Melanoma-associated retinopathy</td>
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<tr>
<td>Optic neuropathy</td>
<td>Bilateral diffuse uveal melanocytic proliferation</td>
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NMDA, N-methyl-d-aspartate.

poor, with many patients becoming non-ambulatory within 3 months (13,14). Most patients have been reported to die of neurologic causes (10,15), but Rojas et al (13) found this to be the case in only 29%.

PCD associated with Hodgkin disease is more commonly found in men with a median age of 54 years, reflecting the bimodal age distribution of Hodgkin disease—one peak occurring in young adulthood and a second peak occurring after age 50 (16). In addition to the cerebellar symptoms of anti-Tr PCD and Hodgkin disease, neuro-ophthalmologic manifestations include downbeat nystagmus, diplopia, oscillopsia, and vertigo. Bernal et al (17) reported that 2 of 28 patients with anti-Tr PCD developed reversible encephalopathy and optic neuritis. The overall prognosis of anti-Tr PCD is better than that of anti-Yo PCD. In one review of 50 cases of PCD (14), patients with anti-Tr PCD had a median survival from time of diagnosis of longer than 117 months compared with patients with anti-Yo PCD, for whom median survival from time of diagnosis was only 13 months.

PCD associated with small-cell lung cancer (SCLC) usually relates to several paraneoplastic antibodies, including anti-Hu, voltage-gated calcium channel (VGCC) antibodies, and infrequently anti-CV2/collapsin response-mediating protein-5 (CRMP-5). Patients with anti-Hu antibodies may present with subacute cerebellar dysfunction in the seventh decade that initially resembles pure PCD in up to 20% of patients. Eventually these patients develop additional neurologic or neuro-ophthalmologic symptoms of brain stem or limbic encephalitis and peripheral neuropathy (14,18,19). Autonomic dysfunction with the development of unilateral or bilateral tonic pupils has been reported in patients with SCLC and anti-Hu antibodies (20–22). Neurologic outcome is generally poor; 75% of patients become bedridden with a median survival of 7–11 months (14,18). Patients with PCD and SCLC who do not have anti-Hu antibodies often harbor VGCC antibodies. These patients may have overlapping manifestations of Lambert-Eaton myasthenic syndrome (see below) (19,23).

For all immunologic types of PCD, CSF studies may show a mild lymphocytic pleocytosis with elevated protein, oligoclonal bands, elevated immunoglobulin synthesis, and negative cytology in approximately 60% of patients. Brain MRI is usually normal at presentation but shows cerebellar atrophy with enlargement of the fourth ventricle and cerebral and cerebellar sulcal prominence in advanced cases (19).

Treatment is directed to the underlying malignancy, although PCD in most patients does not improve with cancer treatment. There are only a few reported cases of improvement or stabilization of PCD after treatment of the neoplasm (15,24–26). Plasmapheresis or immunosuppression (cyclophosphamide or corticosteroids), sometimes used in conjunction with intravenous immunoglobulin (IVIg) and tumor treatment, have shown improvement in several reports (27,28). A study suggested that the likelihood of neurologic improvement after IVIg treatment is higher in those treated within the first month of developing cerebellar dysfunction (29,30).

PARANEOPlastic BRAIN STEM ENCEPHALITIS

Brain stem encephalitis due to paraneoplastic disease can present with various neurologic and neuro-ophthalmologic symptoms and signs, depending on whether the rostral or caudal portions of the brain stem are involved. When midbrain brain stem structures are involved, patients may have palsy, vertical gaze paresis, and nystagmus (31). Pontine and medullary damage can result in vertigo, hearing loss, facial numbness, dysphagia, dysarthria, and hoarseness. Patients may complain of diplopia and oscillopsia with signs of vertical nystagmus, upbeat or downbeat nystagmus, horizontal gaze paresis, internuclear ophthalmoplegia, skew deviation, sixth cranial nerve paresis, impairment of facial sensation, hyperactive gag reflex or jaw jerk, and weakness of the tongue or palatal muscles (8). The antibodies frequently associated with paraneoplastic brain stem encephalitis include Hu, CV2/CRMP-5, Ma-2, and NMDA receptor.

PARANEOPlastic ENCEPHALOmyelitis

Paraneoplastic encephalomyelitis (PEM) refers to an immune-mediated inflammatory disorder that affects the
TABLE 2. Anti-neuronal antibodies with associated tumors and paraneoplastic syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Associated cancer</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu (ANNA-1)</td>
<td>Small cell lung cancer, other</td>
<td>Ependymalitis, brain stem encephalitis, paraneoplastic cerebellar degeneration, sensory neuropathy, autonomic dysfunction</td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>Ovary, breast</td>
<td>Paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>Breast, small cell lung cancer</td>
<td>Paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Hodgkin lymphoma</td>
<td>Paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Testicular germ cell tumor, others</td>
<td>Limbic and brain stem encephalitis</td>
</tr>
<tr>
<td>Anti-amphiphysin</td>
<td>Breast, small cell lung cancer</td>
<td>Stiff-person syndrome, ependymalitis</td>
</tr>
<tr>
<td>Anti-CRMP-5 (anti-CV2)</td>
<td>Small cell lung cancer, other</td>
<td>Ependymalitis, paraneoplastic cerebellar degeneration, peripheral neuropathy, paraneoplastic optic neuropathy</td>
</tr>
<tr>
<td>Anti-NMDA receptor</td>
<td>Teratoma</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Anti-P/Q type voltage-gated</td>
<td>Small cell lung cancer</td>
<td>Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>calcium channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-acetylcholine receptor</td>
<td>Thymoma</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Anti-recoverin</td>
<td>Small cell lung cancer</td>
<td>Cancer-associated retinopathy</td>
</tr>
<tr>
<td>Anti-bipolar cells</td>
<td>Melanoma</td>
<td>Melanoma-associated retinopathy</td>
</tr>
</tbody>
</table>

ANNA, anti-neuronal nuclear antibody; PCA-1, purkinje cell antibody-1; NMDA, N-methyl-d-aspartate; CRMP-5, collapsin response-mediating protein-5.

central nervous system, dorsal root ganglia, and autonomic nerves. Neuro-ophthalmologic findings are common in patients with predominantly brain stem and cerebellar dysfunction. The antibody most frequently encountered is anti-Hu, and the underlying tumor is usually SCLC.

ANTI-MA2 ENCEPHALITIS

Anti-Ma2 encephalitis is characteristically associated with limbic, diencephalic, and brain stem dysfunction. In young men, the tumor most frequently involved is a germ-cell neoplasm of the testis; in older men and women, lung and breast cancers are the predominant tumors (32,33).

In a study of 38 patients with anti-Ma2 encephalitis (32), 25 had brain stem signs; 92% of these patients had eye movement abnormalities, and 60% had vertical gaze paresis that eventually developed into severe or total paralysis. Most patients initially developed difficulty with upward saccades, but a few patients presented with downward gaze paresis. Vestibulo-ocular reflexes and the Bell phenomenon were usually preserved until later in the disease. Ptosis was present in almost 20% of the patients, but the exact mechanism was not elucidated. We have seen patients with paraneoplastic syndromes presenting with apraxia of eyelid opening and ptosis; the latter may relate to loss of neurons in the central caudal subnucleus of the oculomotor nucleus (31). Other neuro-ophthalmologic findings were oculogyric crisis, opsoclonus, ocular flutter, and nystagmus. Bennett et al (34) reported two patients with anti-Ma2 encephalitis who had supranuclear gaze palsy, skew deviation, and an ocular tilt reaction. One patient had bilateral visual loss related to a chronic inflammatory infiltrate that involved the diencephalon, established by brain biopsy; the other patient had upbeat nystagmus in downgaze and a monocular pendular nystagmus. Less common neurologic manifestations in anti-Ma2 encephalitis include parkinsonism and a severe hypokinetic syndrome.

Brain MRI typically shows T2/FLAIR hyperintensities in the brain stem and limbic structures that may enhance on postcontrast T1 sequences (32). In a review of 38 cases (35), 16% of patients with anti-Ma2 encephalitis had been initially considered to have Whipple disease and had undergone duodenal biopsy.

In most patients with testicular cancer, the tumor is identified clinically or by ultrasound, but Mathew et al (36) described six men younger than age 50 who had no evidence of tumor in the setting of anti-Ma2 progressive neurologic deficits. After orchiectomy, all six were found to have a microscopic intratubular germ-cell neoplasm of unclassified type (IGCNU), a common precursor of testicular cancers.

Aggressive search for and treatment of the underlying malignancy in this disorder is important because about one third of patients show improvement after tumor removal.
and immunotherapy, which may include corticosteroids, IVIg, or plasma exchange (32,37).

**ANTI-NMDA RECEPTOR ENCEPHALITIS**

Patients with this disorder develop a highly characteristic syndrome that evolves in stages, consisting of a prodromal low-grade fever and headache followed by prominent psychiatric symptoms or short-term memory loss, along with visual hallucinations, seizures, progressive unresponsiveness, hypoventilation, autonomic instability, and dyskinesias. The disorder usually affects young women with mature or immature ovarian teratomas. All patients harbor serum and CSF antibodies to NR1/NR2 heteromers of the NMDA receptor (38). Some patients present with oculogyric crises in association with orofacial and limb dyskinesias. Opsoclonus has also been observed in some patients with mature teratomas without antibodies to the NMDA receptor. In addition, a patient developed transient inverse ocular bobbing (also known as ocular dipping) while she was in the intensive care unit recovering from anti-NMDA receptor encephalitis (H. Shimazaki, MD, written communication, November 2007). Despite the severity of the disorder, patients usually recover after tumor removal and immunomodulation.

**OPSOCLONUS-MYOCLONUS SYNDROME**

Opsoclonus, which may be of metabolic, infectious, or paraneoplastic origin, consists of involuntary, arrhythmic, multidirectional saccades that are irregular in amplitude and frequency without an intersaccadic interval (39). In a paraneoplastic setting, it generally includes encephalitis, myoclonus, and ataxia of the trunk and limbs [opsoclonus-myoclonus syndrome (OMS)]. The most common underlying malignancy in children with this syndrome is neuroblastoma. Children (more often girls) generally are seen between the ages of 8 months and 3 years with a peak incidence at 18 months (40,41). More than 50% of children with opsoclonus have neuroblastoma, whereas only 2% of children with neuroblastoma present with OMS (41). In adults, there is no gender predilection. Occult malignancies are found in approximately 20% of adults presenting with opsoclonus (42), most often involving the lung (especially SCLC), ovaries, uterus, or breast. OMS associated with thymoma and melanoma has been reported (43,44).

Patients with paraneoplastic OMS are often seronegative for anti-neuronal antibodies; exceptions include those with OMS associated with anti-Ri (45-47) and anti-amphiphysin antibodies (48). Reports of patients with opsoclonus and cerebellar or brain stem encephalitis associated with anti-Hu (49-51), anti-Yo (10), and anti-Ma2 (32) are rare. The pathophysiology of OMS is unknown, but it is suspected to be of autoimmune origin, supported by the detection of CSF inflammatory findings, a clinical response to immunotherapy, and the presence of anti-neuronal antibodies in serum and CSF (48).

Management of OMS involves an aggressive search for an underlying neoplasm and its treatment. Because neuroblastoma is so commonly associated with opsoclonus in children, it is imperative to exclude it. A complete screening protocol for neuroblastoma in a child with opsoclonus or ocular flutter would include 1) urine vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels, 2) MRI of neck, chest, abdomen, and pelvis, and 3) metaiodobenyzylguanidine (MIBG) whole-body scintigraphy if results of MRI are unrevealing.

<table>
<thead>
<tr>
<th>Neuro-ophthalmologic findings</th>
<th>Anti-Yo</th>
<th>Anti-Hu</th>
<th>Anti-Ma2</th>
<th>Anti-Ri</th>
<th>Anti-VGCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal saccades</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ MG</td>
</tr>
<tr>
<td>External ophthalmoplegia</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Eyelid retraction</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td>+ ±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Nystagmus</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ocular dysmetria</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Oculogyric crisis</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Opsoclonus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Optic disc edema</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Optic neuritis</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Photopsias</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Progressive visual loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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</tbody>
</table>

†, downbeat; ↔, horizontal; VGCC, voltage-gated calcium channel; CRMP-5, collapsin response-mediating protein-5; NMDA, N-methyl-d-aspartate; *Rare presentation.
The combination of MRI and MIBG may be necessary because false-negative and -positive results can occur with each test in this setting (52). Standard treatment of children with OMS includes corticosteroids, such as prednisone and adrenocorticotropic hormone (ACTH), which provide some symptomatic improvement but are often associated with long-term adverse side effects (53,54). Rostasy et al (55) reported the use of high-dose pulse dexamethasone in 11 children with OMS, showing complete and sustained remission in approximately 50% with few side effects. Other treatments reported in children include IVIg, cyclophosphamide, and rituximab (56,57) with variable success. Removal of the neuroblastoma alone has not improved symptoms in most patients (53,58). In adults, there have been a few reports of neoplasm resection leading to complete resolution of OMS (59–61). Corticosteroids are not as effective in reversing adult OMS as in reversing childhood OMS (62). Treatments with reported clinical improvement include clonazepam (63), IVIg (50), and immunoadsorption (64,65).

**LAMBERT-EATON MYASTHENIC SYNDROME**

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction caused by antibodies against the VGCC, resulting in a decrease in acetylcholine release at the presynaptic level. LEMS can present in paraneoplastic or primary autoimmune forms, which have identical clinical and pathophysiologic features. Approximately 50% of patients with LEMS have SCLC, whereas the incidence of LEMS in patients with SCLC is only 3% (66). Patients usually present with proximal muscle weakness, autonomic dysfunction, and decreased deep tendon reflexes.

Unlike myasthenia gravis (MG), in which ptosis and diplopia are common manifestations, such signs and symptoms can occur but are generally considered uncommon in LEMS (67,68). Nonetheless, in a series of 50 patients with LEMS, O’Neill et al (67) reported diplopia in 25 (50%) and ptosis in 27 (54%). In another series of 23 patients with LEMS without coexistent MG (69), more than 78% had diplopia, ptosis, dysarthria, or dysphagia. In 30% of these patients, these features were the chief complaint. This study emphasized the fact that some cases of LEMS may be under-recognized because the neuro-ophthalmic findings are often attributed to MG (69,70). Rudnicki (71) reported a patient with LEMS, SCLC, and VGCC antibodies who had diplopia and ptosis as the only clinical manifestations. These manifestations resolved after chemotherapy without further development of neurologic findings.

Ductional deficits are common in patients with MG but are rare in patients with LEMS, with only three cases reported. Only one of these cases was a patient who had LEMS as the only diagnosis; the other two involved patients with overlapping MG (72–74). Other associated features of LEMS include involuntary eyelid closure (74) and dilated, poorly reactive pupils (75,76). Sluggish pupillary reactivity may be a result of autonomic dysfunction in LEMS (77), a feature that would clinically distinguish it from MG. Another clinical feature that may distinguish LEMS from MG is improvement of ptosis with sustained upgaze in patients with LEMS (78), a phenomenon perhaps due to facilitation of the levator muscle after exercise.

The mainstay of diagnostic evaluation in LEMS is electromyography (EMG), with its characteristic findings of
low amplitude resting compound muscle action potentials (CMAPs), a decremental CMAP with low stimulation rates (2–5 Hz), and an incremental CMAP with high stimulation rates (30–50 Hz). An immunoassay for VGCC antibodies is confirmatory in patients with clinical and electrophysiologic features of LEMS but is not diagnostic by itself.

Central to the management of LEMS is an aggressive search for an underlying malignancy. SCLC may not be readily detected on a chest CT scan because the lesions are often very small. Thus, a more intensive search, including bronchoscopy or PET, may be warranted, especially in high-risk patients (79).

Treatment of the malignancy may improve symptoms of LEMS. If patients are still symptomatic after this treatment, medications that improve neuromuscular transmission, such as acetylcholinesterase inhibitors (pyridostigmine) or aminopyridines (3,4-diaminopyridine), may be effective. IVIg has been shown to improve weakness, but the response is temporary, requiring repeat infusions at regular intervals (80–84). Immunosuppressive agents such as prednisone or azathioprine may begin to show benefits several months after treatment is begun (85–87).

### STIFF-PERSON SYNDROME

Stiff-person syndrome (SPS) is a disease characterized by insidious onset of rigidity of the truncal and proximal limb muscles with intermittent superimposed painful spasms. Symptoms are absent during sleep or anesthesia (88–90). Approximately 80% of patients with SPS have a non-paraneoplastic form of this disorder associated with polyendocrinopathies and antibodies to glutamic acid decarboxylase (GAD). The less common paraneoplastic form of SPS is associated with antibodies to amphiphysin. Malignancies most commonly involved in the paraneoplastic form of SPS are SCLC, breast cancer, and Hodgkin disease (91–93).

Neuro-ophthalmologic findings include gaze-evoked nystagmus, poor saccadic initiation, and impaired smooth pursuit (94). In patients with cerebellar dysfunction, there may be downbeat nystagmus, square-wave jerks, skew deviation, slow and hypometric saccades, and impaired smooth pursuit in downward gaze (95–97). The suspected pathophysiology is dysfunction of GABAergic pathways from anti-GAD antibody activity, particularly involving connections within the cerebellum and with the brain stem (94).

There is a report of SPS occurring in conjunction with MG in a patient with bilateral abduction deficits, nystagmus, impairment of horizontal and vertical saccades, but no ptosis. This patient had almost complete resolution of SPS and myasthenic findings after removal of a thymoma (98).

Treatment centers on baclofen or diazepam, which enhance central gamma-aminobutyric acid (GABA) activity, and immunomodulation. Patients with SPS receiving high-dose IVIg treatment have had reduced stiffness and falls and improved ambulation and performance in work-related or household tasks. The duration of benefits can range from 6 weeks to 1 year (99–101).

### CANCER-ASSOCIATED RETINOPATHY

Cancer-associated retinopathy (CAR) was first recognized in three patients who had a visual disturbance before the diagnosis of their cancers (102). Autopsy findings showed photoreceptor degeneration without coexistent neoplastic involvement of the orbit, eye, or optic nerve. In the early 1980s, Keltner et al (103) reported a patient with paraneoplastic retinopathy and demonstrated retinal antibodies reacting against photoreceptor cells. In a series of three patients with CAR, Thirkell et al (104) found an antibody that bound to a 23-kDa retinal antigen. It was later named “recoverin” and identified as a Ca²⁺-binding photoreceptor protein that controls phosphorylation of the visual receptor rhodopsin by inhibition of rhodopsin kinase (105). Although recoverin is the most common antigen linked with CAR, more than 20 other antigens have since been identified, including a 65-kDa heat shock cognate protein (106), a 48-kDa protein (107), an enolase (108), a photoreceptor nuclear receptor (109), and neurofilaments (110). These findings suggest that CAR represents the clinical manifestations of a multiplicity of autoimmune reactions (8,111).

Patients with CAR generally present with symptoms of painless progressive visual dimming and photopsias. They have a constellation of visual symptoms attributable to rod dysfunction (impaired dark adaptation and peripheral visual field loss) and cone dysfunction (decreased visual acuity, central scotomas, color dysfunction, photosensitivity, and glare after light exposure).

On examination, patients have bilateral ocular involvement with a decrease in visual acuity, color discrimination, and visual field that includes central or ring scotomas with preserved islands of vision. Results of ophthalmoscopy at symptom onset may be unremarkable but shortly thereafter may show arteriolar narrowing, retinal pigment epithelial alteration with thinning and mottling, and optic disc pallor. Vitreous and anterior chamber cells may be seen. Electroretinography (ERG) shows undetectable or substantially decreased responses due to photoreceptor degeneration. Results of CSF studies can range from normal to showing mild lymphocytic pleocytosis and elevated protein.

CAR is most commonly associated with SCLC and less commonly with non-small cell lung, ovarian, cervical, and endometrial cancers. Rare reports of colon carcinoma (112) and invasive thymoma (113,114) have also appeared.
For many years, corticosteroids were the mainstay of treatment but produced disappointing results. Guy and Aptsiauri (115) reported two patients with a mild to moderate response to IVIg. Espandar et al (116) have reported a patient with CAR who had a favorable response to alemtuzumab, a monoclonal antibody against the cell surface glycoprotein CD52 expressed on B and T lymphocytes, monocytes, and macrophages. The patient's symptoms had not improved after plasma exchange and cyclosporine treatment, but for 8 years the patient had several episodes of relapsing-remitting retinopathy, which improved each time after alemtuzumab treatment. Much more study will be needed to determine whether any of these treatments is truly effective.

MELANOMA-ASSOCIATED RETINOPATHY

Melanoma-associated retinopathy (MAR) is a rare visual paraneoplastic syndrome with fewer than 100 reported cases (117–119). Patients with MAR frequently have an established diagnosis of cutaneous melanoma with visual problems developing months to years later. There is never any evidence of ocular or other metastasis at the time that visual symptoms begin. The proposed pathophysiology involves a B-lymphocyte response to the production of autoantibodies against an unknown melanoma antigen that cross-reacts with retinal components, particularly bipolar cells (120–122).

In a review of 62 cases, Keltner et al (117) found that the average patient age at presentation was 57.5 years, ranging from 30 to 78 years. Men were more frequently affected than woman, and visual acuity at presentation was 20/60 or better in 82% of patients. Common symptoms included shimmering, flickering or pulsating photopsias, progressive vision loss over months, and night blindness.

MAR differs from CAR in that visual acuity and color vision are usually normal or near normal (Table 4). Initial fundus findings may be normal, but retinal vessel narrowing, retinal pigment epithelium changes, and optic disc pallor have been noted several months after presentation. Although manifestations may initially be limited to one eye, the disorder eventually affects both eyes within weeks to months. Visual fields may be completely normal or show peripheral constriction, generalized depression, or paracentral or mid-peripheral scotomas. Central scotomas are less common in MAR than in CAR. The ERG shows reduced or absent b-waves with normal dark-adapted a-waves indicating bipolar cell dysfunction (123,124). CSF constituents are normal.

There is no certifiably effective treatment for MAR. Radiation therapy, IVIg, cytoreductive (debulking) surgery, and intravenous (IV) corticosteroids with plasmapheresis have been associated with improved visual acuity and visual field (117). In the large review by Keltner et al (117), four of seven patients with MAR who experienced visual improvement had undergone cytoreductive surgery, received IVIg, or both. Corticosteroids alone have not been associated with symptomatic improvement. Reducing the tumor burden may be important, as emphasized by the case of a patient who had worsening visual acuity every time metastases recurred and improvement when radiation therapy reduced the size of the metastases (117).

PARANEOPLASTIC OPTIC NEUROPATHY

Paraneoplastic optic neuropathy (123) is a rare disorder characterized by painless visual loss and optic disc edema. Associated manifestations may include ophthalmoplegia (125,126), retinitis (127), subacute cerebellar syndrome (128–132), and other neurologic deficits.

<table>
<thead>
<tr>
<th>TABLE 4. Comparison of cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR)</th>
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<tbody>
<tr>
<td><strong>CAR</strong></td>
</tr>
<tr>
<td>Presenting age (range)</td>
</tr>
<tr>
<td>Gender predilection</td>
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<tr>
<td>Presenting visual acuity</td>
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<tr>
<td>Timing of ophthalmic manifestations in relation to diagnosis of malignancy</td>
</tr>
<tr>
<td>Ophthalmoscopy</td>
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<tr>
<td>Electoretinography</td>
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<tr>
<td>Survival time after cancer diagnosis</td>
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Patients with PON present between the ages of 50 and 75 years with a history of heavy smoking; men and women are equally affected. Painless visual loss occurs over weeks to months, ultimately involving both eyes. Most patients also have ataxia, movement disorders, cranial nerve abnormalities, cognitive impairment, seizures, neuropathy, autonomic instability, or myelopathy. Neuro-ophthalmologic manifestations include vertical gaze paresis, optic neuritis, and bilateral internuclear opthalmoplegia (127, 129). Edematous optic discs, vitreous cells, and visual field defects are often present on examination. The paraneoplastic antibody most frequently identified is CV2/CRMP-5.

Mild enhancement of the optic nerve has been reported on MRI (133). Fluorescein angiography may show optic disc hyperfluorescence and leakage. Full-field ERG has shown prolongation of the scotopic combined rod-cone response, the photopic cone response, and the photopic 30-Hz flicker response (127). Based on the small number of patients, the neurologic and visual prognosis for PON seems to be dependent on how well patients have responded to treatment of their underlying malignancy (131, 132).

BILATERAL DIFFUSE UVEAL MELANOCYTIC PROLIFERATION

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is an uncommon paraneoplastic entity in which an underlying tumor causes diffuse bilateral proliferation of melanocytes in the uveal tract, leading to bilateral visual loss. Approximately 30 cases have been reported (134, 135).

BDUMP was first described in 1966 by Machemer (136) in a 57-year-old man with bilateral visual loss, cataracts, and retinal detachments. The histopathology of the eyes showed diffuse choroidal and ciliary body thickening. The patient had a retroperitoneal mass suspected to be a pancreatic cancer, but a postmortem study was never performed because the patient died several days after exploratory laparotomy.

In women, carcinoma of the reproductive tract is often found; in men, carcinomas of the lung and pancreas are most common. Visual acuity ranges from normal to light perception. Gass et al. (137) described multiple red retinal pigment epithelium (RPE) patches in the posterior pole with early fluorescein angiographic hyperfluorescence, together with multiple slightly elevated uveal melanocytic tumors and diffuse uveal tract thickening, exudative retinal detachment, and rapidly progressive cataract.

Patients of either sex generally present after age 50 with abrupt bilateral visual loss and few or no fundus findings but may range in age from 34 to 89 years. Nearly all patients have had rapid cataract progression, and all have had retinal detachment (135). The visual symptoms precede the diagnosis of a systemic malignancy. Although choroidal thickening may be diffuse on pathologic examination, it appears focal on ophthalmoscopic examination.

Some observers believe that the uveal manifestations of BDUMP represent a benign entity without a tendency to metastasize (138). This assumption has been based on the fact that most reported patients have benign-appearing melanocytes and no evidence of uveal tract metastasis. Lack of uveal melanocytic spread could be related to short survival, which might preclude identification of metastasis. In one review, the average time from presentation to death was a mean of 15 months. Some observers believe, however, that the uveal manifestations of BDUMP have metastatic potential (139). Duong et al. (140) reported a patient with BDUMP associated with ovarian carcinoma who survived the ovarian cancer, but subsequently developed metastatic amelanotic malignant melanoma.

In the earliest reported cases of BDUMP, patients’ choroidal lesions were irradiated in the belief that they were malignancies, a treatment that was sometimes associated with worsening of vision. Corticosteroid treatment has also been used without visual improvement. One case report ascribed improvement in vision to treatment with external beam irradiation and subretinal fluid drainage (141).

Acknowledgments

The authors thank the following physicians who generously contributed to this manuscript: Dr. Grant Liu, Dr. Myrna Rosenfeld, and Dr. Shawn Bird.

REFERENCES


