North American Neuro-Ophthalmology Society
36th Annual Meeting
March 6-11, 2010 • JW Starr Pass Marriott Resort & Spa, Tucson, AZ
Educational Program Schedule

**WEDNESDAY, MARCH 10**

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<td>Registration</td>
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<td>6:30 a.m. - 7:30 a.m.</td>
<td>Continental Breakfast</td>
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<td>7:00 a.m. - 7:30 a.m.</td>
<td>Annual NANOS Business Meeting (all encouraged to attend)</td>
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<td>7:30 a.m. - 11:35 a.m.</td>
<td>NEURO–OPHTHALMOLOGY OF CANCER [3.25 CME]</td>
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*Moderators: Larry Frohman, MD and Mark Moster, MD*

The full morning symposium will review and update knowledge concerning the neuro–ophthalmologic disorders related to systemic cancer. This session will include an update on the treatment of primary and metastatic CNS tumors. The neuro–ophthalmologic complications of stem cell and bone marrow transplantation will be described. There will be a discussion of the effects on the afferent visual system of radiotherapy, as well as a separate session on the disorders of eye movement that can result from radiotherapy.

The neuro–ophthalmologic complications of the treatment of cancer with chemotherapeutic agents will be covered in detail. Paraneoplastic syndromes with neuro–ophthalmologic manifestations will be discussed, with separate treatment of those affecting the afferent visual system (retina and optic nerve, especially), and those effecting ocular motor structures.

At the conclusion of the symposium, the attendees should be able to: 1) Discuss the current treatment options for primary and secondary CNS malignancy; 2) Describe the major neuro–ophthalmologic complications of stem cell and bone marrow transplantation therapy; 3) Discuss the effects of radiotherapy on the retina and optic nerves; 4) Explain the complications of systemic chemotherapy involving visual function; 5) Discuss the neuro–ophthalmologic manifestations of paraneoplastic syndromes.

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<td>7:35 a.m. - 8:25 a.m.</td>
<td>Update On Treatment of Primary and Secondary Central Nervous System Tumors – Amy Pruitt, MD</td>
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<td>Paraneoplastic Retinopathies and Optic Neuropathies vs. (NON–CANCER) Autoimmune related retinopathy and optic neuropathy (ARRON Syndrome) – John Keltner, MD</td>
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<td>Ocular Motor Complications of Radiation Therapy – Valerie Purvin, MD</td>
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| 11:35 a.m. - 12:20 p.m. | **JACOBSON LECTURE [.75 CME]**
IlH with Dan, and Beyond – Deborah I. Friedman, MD | Arizona Salons 1–6 |
| 12:30 p.m. - 4:00 p.m.   | **PRACTICE MANAGEMENT SYMPOSIUM [3 CME]**
How to Earn Money in the Post–Consult World – Stephen M. Sadowski | Arizona Salons 1–6 |
| 12:20 p.m. - 1:15 p.m.   | Fellows-in-training Forum: Advice for the Job Search | Arizona Salon 10 |
| 1:15 p.m. - 2:15 p.m.    | Neuro-Ophthalmology New Attendings Forum:
Advice for the First Few Years | Arizona Salon 10 |
| 4:00 p.m. - 5:30 p.m.    | **BOTULINUM TOXIN IN NEURO–OPHTHALMOLOGY**
Wayne Cornblath, MD
A review of the uses of botulinum toxin in neuro-ophthalmology including discussion of injection technique, dosage and billing for blepharospasm, hemifacial spasm, crocodile tears and headache.
At the conclusion of the symposium, the attendees should be able to: 1) Learn how to diagnosis blepharospasm and hemifacial spasm; 2) Review injection technique and patterns for BEB and HFS; 3) Review the use of botulinum toxin in treatment of headache; and 4) Review injection technique and pattern for headache treatment. | Arizona Salons 1–6 |
| 7:00 p.m. - 11:00 p.m.   | Annual NANOS Reception and Banquet
Buses depart from main lobby at 5:15 p.m. and 6:30 p.m. | Pima Air and Space Museum |
LEARNING OBJECTIVES

It is understood that a neuro-ophthalmologist is unlikely to be the primary physician for patients with CNS tumors, but neuro-ophthalmologists are called upon to see such patients at all stages of their illness, including at presentation for such tumors as primary retinal lymphoma, optic nerve gliomas and meningiomas. Therefore, ophthalmologic specialists must know the likely behavior of the relevant neoplasm, its prognosis, and its treatment in order to diagnose accurately and to provide timely referral and management. For each neoplasm discussed, the syllabus and lecture will provide information on epidemiology, current standard of care, investigational trials, and special issues of concern to neuro-ophthalmologists.

After reviewing these materials and the accompanying lecture attendees will be able to:

1. Describe the epidemiology, risk factors, and standard of care for common adult primary and secondary CNS tumors, including glioblastoma, anaplastic astrocytoma, oligodendroglioma and other low-grade gliomas, meningioma, primary CNS lymphoma, and secondary tumors, particularly lung and breast primary malignancies.

2. Understand the molecular underpinnings and evidence base for current investigational trials of brain tumor treatment and direct patients to relevant Internet sites.

3. Provide timely evaluation and management of acute and long-term medical complications of primary and metastatic nervous system tumors with particular attention to vision-involving acute and chronic adverse effects of chemotherapy and radiation including such recently described conditions as altered recurrence pattern with anti-angiogenic agents, pseudo-progression, reversible posterior leukoencephalopathy syndrome, immune reconstitution, and "stroke-like migraines”.

CME QUESTIONS

1. The current standard of care for glioblastoma initial treatment is:
   a. Radiation therapy to involved area of brain.
   b. Chemoradiation with concurrent temozolomide and radiation therapy followed by monthly cycles of temozolomide.
   c. Bevacizumab and temozolomide along with radiation therapy followed by monthly cycles of temozolomide.
   d. Procarbazine, CCNU, and vincristine along with radiation therapy.
   e. Stereotactic radiosurgery and high dose methotrexate.

2. A patient who received oxaliplatin, 5-fluorouracil, and bevacizumab for colon carcinoma one day earlier becomes confused and behaves as if he cannot see. His pupils are reactive and he appears to be unable to navigate around his environment. Blood pressure is 180/110. His MRI is most likely to show:
   a. Bilateral posterior cerebral artery strokes
   b. Papilledema
   c. Vasogenic edema in posterior hemispheres
   d. Multiple cerebral metastases
   e. Progressive multifocal leukoencephalopathy

3. A 67 year old man presents with blurred vision in his right eye. A diagnosis of intraocular lymphoma is considered. The next step in diagnosis should be:
   a. Vitrectomy
   b. Chest, abdominal and pelvic computed tomographic (ct) scans
   c. Bone marrow biopsy
   d. Positron emission tomographic (pet) body scan
   e. MRI of the brain

KEY WORDS

1. Bevacizumab
2. Glioblastoma
3. Meningioma
4. Oligodendroglioma
5. Posterior reversible encephalopathy syndrome
6. Primary intraocular lymphoma
INTRODUCTION
During the past few years there have been significant advances in the molecular understanding of primary brain tumors, important enhancements in diagnostic imaging techniques, and a pipeline of novel agents from preclinical studies. While these developments have produced only modest improvements in outcomes for patients with central nervous system malignancies, novel investigational approaches to brain tumor therapy are beginning to offer hope to these patients whose prognosis often is quite grim.

GENERAL OVERVIEW OF PRIMARY BRAIN TUMORS
Epidemiology
According to the Central Brain Tumor Registry of the United States (CBTRUS) 2005, approximately 43,800 new primary central nervous system (CNS) tumors are diagnosed annually. About one third of these are malignant gliomas, neither of which misleading word should be used routinely in a discussion with patients and their families. With the possible exception of resectable meningiomas, all CNS tumors have the capacity to cause disability and shorten life expectancy and, therefore, are not benign. Glioma is a generic term for several different histologies of primary tumor (astrocytoma, oligodendroglioma, ependymoma, and choroid plexus papilloma, each with a different prognosis and therapy). Therefore, the clinician should speak cautiously and specifically when counseling brain tumor patients and should direct them to reputable information sources.

Patients will want access to brain tumor centers and clinical trial protocol sites. The following websites and publications will help your patients get started.

National Cancer Institute guidebook: Taking Part in Clinical Trials: What Cancer Patients Need to Know. Website: http://www.nci.nih.gov Phone: 1-800-4-CANCER
- OncoLink: www.oncolink.upenn.edu
- Johns Hopkins Neurology/Neurosurgery: http://www.ed.jhu.edu/neurology
- Columbia: http://cpmcnet.columbia.edu/dep/neurology/cent0005.html
- National Brain Tumor Foundation: http://www.braintumororg.com
- American Brain Tumor Association: http://www.abta.org
- People Living with Cancer (pain, palliative, patient-friendly): http://www.plwc.org

CNS tumors are the 2nd leading cause of cancer death in children and the 5th in young adults. High-grade gliomas are the 3rd leading cause of cancer death in adults age 15–34. CNS tumors represent 2.5% of all deaths due to cancer, exceeding the numbers of deaths from Hodgkin’s disease and nearly equaling those from ovarian cancer. There appears to be a significant increase in primary brain tumors among the elderly, particularly in those over age 85 that is not paralleled by a comparable increase in brain tumor incidence in the middle-aged population.1 According to SEER (Surveillance, Epidemiology and End Results of the National Cancer Institute) data, between 1991 and 1995, malignant tumors of the brain and spinal cord comprised 1% of newly diagnosed adult cancers and 2.5% of cancer deaths.2

The fourth edition of the World Health Organization classification of CNS tumors was published in 2007 and lists several new entities, variants, and patterns. As of this update, molecular neuropathology markers that confer prognostic significance (MGMT promoter gene methylation and 1p/19q co–deletions) are not incorporated into the classification system, but have begun to be used to stratify patients for ongoing clinical trials.3

Risk Factors
Five percent of patients with malignant primary brain tumors have a family history of glial tumor. Johns Hopkins maintains a data base of familial primary brain tumors and an international consortium called GLIOGENE has been established to study the genetic basis of familial gliomas. The major hereditary conditions associated with an excess risk of adult brain tumors in the immunocompetent population are summarized in the table on the following page.
Additional risk factors for brain tumors include prior radiation exposure (meningiomas, astrocytomas) immunosuppression (45-fold elevated risk of glial tumor in HIV patients while elevated IgE levels, asthma and eczema are negative risk factors). At this time, no study has convincingly demonstrated that the use of cellular telephones poses a significant risk for glioma or meningioma.

### High-Grade Astrocytomas (Glioblastoma and Anaplastic Astrocytoma)

**Epidemiology**
Malignant glial tumors are 40% more common in men as in women and twice as common in whites as in blacks. Etiology remains unknown. Glioblastomas account for approximately 60% of high-grade primary tumors. The median age of patients at the time of diagnosis of glioblastoma (GBM) is 64 years and 45 years for anaplastic gliomas. GBM may develop de novo (primary GBM) or via progression from low-grade or anaplastic astrocytoma (secondary GBM). Mean age of primary GBM is greater than that of patients with a history of prior low grade astrocytic tumor. Recent information from genome-wide mutation analysis of GBM revealed somatic mutations of the isocitrate dehydrogenase 1 gene in the majority of low-grade tumors and in 12% of those evolved form lower grade tumors. Such mutations correlated with longer survival, perhaps in part explaining the age-related prognosis of these neoplasms.

### Standard of Care
Survival correlates with age at diagnosis, tumor grade, and, most importantly, with post-resection tumor volume. MRS and fMRI guided surgical resection, viewing wand, stealth procedures, intraoperative MRI, and diffusion tensor imaging are recent techniques that enhance the degree of surgical extirpation. After surgical resection, radiation with concurrent chemotherapy with the alkylating agent temozolomide has been the standard of care since the seminal studies by Stupp and Hegi in 2004–2005. These studies were accompanied by translation research that identified methylation of the promoter of a DNA repair enzyme, MGMT, as a predictor of response to chemotherapy.

The current standard of care is:

1. Maximal feasible resection—(for some clinical trials, MGMT promoter methylation status)
2. Concurrent radiation therapy and low-dose temozolomide
Investigational Strategies
Despite the above protocol which has led to a 48% 2 year survival in patients with a methylated MGMT promoter gene and to a 4 year survival in patients under age 50 with these molecular characteristics of 28%, essentially all these tumors recur. Investigational strategies include the incorporation of molecular markers into clinical trials and to the use of novel tyrosine kinase inhibitors and/or angiogenesis blockers. The most important new drug of the past two years is bevacizumab (Avastin) whose ability to reduce markedly the amount of vasogenic edema with rapid improvement in MRI scans has led to an explosion of its use. Concerns are developing, however, about a difference in recurrence pattern. The case below illustrates the dilemmas of diagnosis, therapy and treatment toxicity at each stage in an astrocytic tumor.

CASE: Secondary Glioblastoma after 18 years
At age 40 the patient had a first seizure and MRI revealed nonenhancing parietotemporal mass. Biopsy demonstrated grade II astrocytoma. He declined further therapy until growth by 1999 resulted in more seizures. Partial resection of tumor was effected. The tumor grew on procarbazine, CCNU, and vincristine chemotherapy, but radiation provided stability through 2001 when, now with some enhancement, tumor was treated with temozolomide 5/28 days and then carboplatin. Patient was stable through early 2008. Dose-intensified temozolomide 21/28 days caused minimal regression of a now vividly-enhancing lesion which by MRS c/w high-grade tumor. Bevacizumab was given for several cycles, but patient’s clinical condition deteriorated with regression of enhancing tumor but progression of NONenhancing signal on MRI. Decadron and carboplatin were instituted. At postmortem there was multilobar infiltration by tumor and leptomeningeal dissemination.

High-Grade Tumors: Neuro-ophthalmologic Issues:
Bevacizumab
Pseudo-progression
Complications of corticosteroids

LOW-GRADE GLIAL TUMORS
(ASTROCYTOMA, OLIGOASTROCYTOMA, OLIGODENDROGLIOMA, ADULT BRAINSTEM GLIOMA, OPTIC NERVE GLIOMA)

Epidemiology
Low-grade gliomas account for 40% of glial tumors with a median age of about 40. There are no evidence based guidelines for these patients, but demographic studies have provided some perspective. Detailed population-based estimates of long-term survival as well as patterns of care for patients with low-grade gliomas examined by age at diagnosis, gender, race and year of diagnosis have not been widely available until the excellent publication by Claus and Black in 2006. Data for patients diagnosed with low-grade gliomas (A, OA, O) between 1973 and 2001 are presented that suggest several trends.
The frequency of histologic diagnosis of oligodendroglioma and oligoastrocytoma has gone up. The first course of treatment has reflected a decrease in radiation only and a marked increase in surgery only with a decrease in radiation and surgery as initial combined therapy. Importantly, 25% of the patients in these data survived for 2 decades, making it imperative to weigh the risks of radiation therapy and chemotherapy against the long natural course of the disease. Quality-of-life features including seizures and cognitive changes will be emphasized in the lecture. A major need is for better therapies for cognitive impairment associated with these low-grade tumors. Donepezil and modafenil have been tried with modest success.

Standard of Care

Oligodendroglioma: The following recommendations can be considered level C evidence-based guidelines, as many clinical trials have too few patients or too disparate surgical and performance status bases to make the evidence more compelling. Patients should have maximal resection with analysis for 1p and 19q abnormalities followed by consideration of clinical trial entry or radiation therapy in patients over age 40 and by conservative follow-up with MRI imaging for younger patients. The benefits of radiation therapy in younger patients remain unclear as median survival in low-grade oligodendrogliomas is 11 years and 5 year survival is 89%. Temozolomide can be considered as an alternative to radiation therapy at the time of progression with continued progression after 2 cycles an indication for radiation therapy. Though the objection radiographic response rate is relatively low at 17% PR and 14% minor response, 51% of patients in a recent study improved, primarily from the point of view of reduction in seizure activity. As more tumors are studied for chromosomal markers, additional stratification of patients may be possible. An interesting observation is the correlation of localization of tumor and growth pattern with genetic signature in oligodendroglial tumors. Patients with insular, diencephalic or temporal lobe lesions were less likely to be 1p/19q positive than those with frontal, parietal or occipital lesions which in turn were often bilateral. These recommendations may apply to mixed histology low-grade tumors (oligoastrocytomas) and to a lesser extent to astrocytomas. The special case of anaplastic oligodendrogliomas will be illustrated in the lecture slides.

Investigational Strategies: Incorporating molecular markers into chemotherapy trials for low-grade gliomas (symptomatic or progressive), ongoing trials compare radiation alone vs temozolomide alone. The not inconsiderable risk of long-term temozolomide in these patients is low CD4 count and thrombocytopenia.

LOW GRADE TUMORS: NEURO-OPHTHALMOLOGIC ISSUES

Brainstem Glioma: Brainstem tumors frequently present with eye movement abnormalities and thus very well may be seen initially by a neuro-ophthalmologist. Unusual multiple sclerosis tumefactive presentations must be considered in the differential and biopsy, though difficult, increasingly is used to be sure of the disease process. Brainstem gliomas are something of an exception to the rule of age conferring a poorer prognosis. Kesari and colleagues looked at the epidemiology of brainstem gliomas and confirmed earlier studies by Guillamo et al that adults have a somewhat better prognosis. Location of a brainstem tumor is all important—long term stability with or without radiation treatment is possible for isolated tectal and cervicomedullary junction tumors, while diffuse pontine gliomas have more rapid progression. Rarely, high-grade tumors present in the brainstem. The differential diagnosis here includes tumefactive multiple sclerosis and, in extremely acute cases, Listeria-related rhombencephalitis. Adults may survive many years after radiation therapy — long enough to have nerve infarcts, myokymia, radiation necrosis and other sequelae to be discussed in detail in another lecture in this session.

Optic Nerve Glioma: Optic nerve gliomas account for 1% of all intracranial tumors. A more correct term is low-grade glioma of the supratentorial midline as these tumors may not be limited to the prechiasmal optic nerve but also involve the chiasm, optic tract or hypothalamus. Nearly 75% are found in children younger than 10 years and may be either completely asymptomatic or cause visual acuity loss, visual field loss, APD, optic atrophy, disc swelling, or, by space occupying volume within the orbit, proptosis, and ocular motility disorders. There is a wide range of estimates of patients with NF 1. The vast majority are pilocytic tumors without mitotic figures. Extension of tumor is more important than histologic appearance, with involvement of chiasm and/or tracts being a bad prognostic sign. Progression after age 12 is unusual. Best support for therapeutic effects comes from retrospective or nonrandomized studies — progressive functional loss not radiographic tumor growth alone should be the main indication for treatment. NF 1 m\patients miss the tumor suppressor gene product neurofibromin tripling the risk of secondary tumors after radiation therapy. Radiation therapy adds additional risks: malignant transformation which otherwise is very rare and moyamoya syndrome which develops a median of 40 months after treatment—risk increased in NF1 and is a function of dosage. Interest in chemotherapy to delay radiation has been directed at younger children and some studies have shown a slightly better progression free survival (PFS) for the chemotherapy group. No direct comparison of the older regimen of vincristine–carboplatin to currently employed temozolomide has been performed.
MENINGIOMAS

Epidemiology
It is appropriate to move to meningiomas after the optic nerve glioma discussion as this is another tumor that may present initially to the neuro-ophthalmologist. Meningiomas represent about 32% of all intracranial adult CNS tumors and are more common in women. We will begin with optic nerve meningiomas. The frequency of optic nerve meningioma among orbital tumors is 8–14%. Malignancy is rare and the histology is usually syncytial or transitional meningioma. The absence of histologic malignancy does not exclude aggressive behavior. There is a relationship between optic nerve meningioma and NF2 (in the coming year or two you likely will be hearing about bevacizumab again both for hearing and visual problems in patients with NF2). In some series as many as 27% of patients with NF2 developed optic nerve meningiomas.

Optic nerve meningiomas occur most commonly in women ages 35–50 with painless progressive visual loss the most common presentation. There are concerns that hormone replacement therapy may increase the risk of meningioma or spur tumor growth.13 Optic nerve meningiomas are bilateral in approximately 10%, perhaps higher in men and in patients with NF2. Unlike in glaucoma, whose nerve fiber bundle defects this tumor may mimic, visual acuity is reduced early on in compressive disease.

Standard of Care
A trial of steroids is often undertaken as the differential diagnosis includes lymphoma and granulomatous inflammation as well as glioma (neither glioma nor meningioma would change significantly with steroids). The Therapeutic approach has changed markedly in past decade. Radiotherapy leads to stability of improvement in a large number of patients. Typical tumor doses are 54Gy. No pseudoprogression has been noted. Radiation-induced optic neuropathy is the major risk.14 Attempts to treat with intravitreal anti–VEGF restored vision in one patient. Target volume planning has been aided by octreotide (DOTATOC) a somatostatin analogue labeled with 68 gallium allowing PET scanning. Surgery is reserved for cases of intracranial extension, severe proptosis or rapid deterioration. There have been few studies of chemotherapy in optic nerve meningioma. In one series that did NOT include optic nerve meningioma, somatostatin has been used for recurrent tumor and mifepristone (RU 486) led to improvement in almost 30% of patients with unresectable meningioma in another small series.15

Other meningiomas: Meningiomas may be classified as WHO grade I (benign) but some are atypical (WHO II or malignant (WHO grade III). They are of interest to neuro-ophthalmologists because those in the optic chiasm, sphenoid ridge skull base and cerebellar tentorium may present with ocular symptoms. Molecular neuropathology with loss of heterozygosity on chromosome 22q is identified as a common genetic event. (The NF2 gene is affected by inactivating mutations in most tumors with LOH 22q). Beyond surgery, radiation therapy is provided as adjuvant therapy following resection of atypical and malignant meningiomas.16 Fractionated stereotactic radiosurgery is considered for those tumors in contact with critical structures such as cranial nerves and brainstem. The role of chemotherapy has been limited to treatment of tumors that recur after surgery and radiation. Efficacy has been disappointing, but agents studied are octreotide, imatinib, interferon alpha, irinotecan, mifepristone, and temozolomide. Hydroxyurea has been evaluated in several series totally about 135 patients with minor or partial radiographic responses in 6% The Southwest Oncology Group’s phase 2 study is currently in progress to further evaluate the role of hydroxyurea in meningiomas. Targeted molecular agents to inhibit signal transduction from activated receptor tyrosine kinases such as epidermal growth factor (EGF) and platelet derived growth factor (PDGFR) are the subject of trials that also include VEGFR inhibitors. Sorafenib and sunitinib are small molecule inhibitors of the VEGF receptor that offer some possible benefit for these highly vascular tumors. In an interim analysis of sunitinib the 6 month PFS for atypical and malignant meningiomas is greater than 50%.17 As meningiomas often occur in women during reproductive years and may be more common among breast cancer patients, exogenous estrogen and progestins have been seen as targets. Estrogen receptors are expressed in about 10% of meningiomas while progesterone receptors and androgen receptors are present in about two-thirds of such tumors. Mifepristone has not been particularly helpful. The association between acromegaly and an increased incidence of meningiomas has focused attention on growth hormone receptors. Pegvisomant, which blocks growth hormone receptor and has been reported to inhibit tumor growth in murine meningioma xenografts, had no impact on one patient. As noted above, somatostatin inhibits meningioma cell growth and such receptors are expressed in nearly 90% of meningiomas. A 31% partial response (Chamberlain above) has been reported with a sustained–release somatostatin preparation. Pasireotide (SOM230) is a somatostatin analogue with wider receptor spectrum currently in trial.

PRIMARY CNS LYMPHOMA (PCNSL) AND PRIMARY INTRAOCULAR LYMPHOMA (PIOL)

Epidemiology
PCNSL is an aggressive B cell nonHodgkin lymphoma, technically a stage IE extranodal (brain meninges, eye) lymphoma, representing about 3% of all primary CNS tumors in the CNS. This discussion will be confined to PCNSL arising in immunocompetent patients and not in the AIDS or transplant recipient groups. Median age of onset is 63 years. Currently one and five year survival rates are 38% and 17.7% respectively. Recommended neurologic staging for a patient with PCNSL includes slit lamp examination, brain RI with gadolinium, CSF
evaluation with cytology, and spinal MRI with gadolinium in patients with symptoms referable to the cord. Though systemic lymphoma is uncommon, patients should have clinical evaluation of lymph nodes, males should have testicular examination and, at times, body CT or PET imaging are used to exclude extranodal sites of disease—disease found in 11% of patients with initially presumed PCNSL. All patients should be tested for HIV infection.

The classic MRI appearance is a homogeneously enhancing mass or masses in the periventricular regions of the brain. Occasionally the tumor may be centrally necrotic and even less commonly there may be diffusely infiltrating lymphomatosis cerebri. Diagnosis of lymphoma may be complicated by the use of steroids before biopsy, but a revision of this stance is evolving. If the patient’s tumor retains contrast enhancement after introduction of steroids, the surgeon is likely to get a diagnosis from biopsy according to a recent Mayo Clinic retrospective study.18

**Standard of Care**

The most important prognostic factors are patient age and performance status. Methotrexate is the most effective chemotherapeutic agent. The optimal dose, duration and treatment regimen are not known. Typically 1–8gm/m² is given systemically. Recently rituximab an anti–CD20 B cell antibody, has been added to this regimen. At relapse, radiation therapy can be considered but there is a high frequency of cognitive deterioration within the year after treatment and often sooner. Temozolomide is emerging as a useful line of therapy in patients relapsing or progressing after methotrexate.19

**Investigational Strategies**

Antilogous stem cell transplantation and salvage regimens including radiation have been employed. Penetrated, a recently approved foliate antagonist, may be used in upcoming clinical trials.

**PCNSL: NEURO-OPHTHALMOLOGIC ISSUES**

Approximately 10% of PCNSL patients present with intraocular lymphoma. Patients with isolated ocular disease may have an insidious onset of decreased visual acuity or vitreal opacities that increase over time. Patients with isolated ocular lymphoma are at high risk to progress to CNS disease and untreated disease in the eye may be a reservoir for recurrence in patients with brain lymphoma. In a recent series of 221 patients with PCNSL involving the eye, PFS and OS were similar to other series of PCNSL. Therapy with radiation or intraocular chemotherapy improved local disease control and led to sustained ocular remissions but did not impact survival.20 Rituximab also may be given intravitreally.21,22 Many of the therapeutic modalities for isolated intraocular lymphoma derive from brain PCNSL protocols. Continuous infusion of high–dose methotrexate yields cytotoxic levels in the anterior chamber of the eye and both methotrexate and cytarabine have activity in intraocular lymphoma. Ocular radiation is effective, but treatment–associated morbidity includes cataracts, retinal damage and visual loss due to ischemic optic neuropathy covered elsewhere in this session.

**Diagnostic approach to Intraocular lymphoma:**

Frequently masquerading as a uveitis, PIOL is misdiagnosed as intraocular inflammation or occasionally as a viral retinitis. Some authors have suggested that primary intraocular lymphoma be renamed primary retinal lymphoma. The integration of clinical, cytologic, and flow cytometric immunophenotyping is emerging as a strategy to classify and prognosticate in this group of patients. Raparia and colleagues found that cases could be classified according to the WHO lymphoma classification by using flow cytometry with a panel of antibodies to CD19, CD20, CD5, CD10 and kappa and lambda light chains. The tumors were mostly diffuse large B cell lymphomas, with less common marginal zone lymphoma of mucosa–associated lymphoid tissue (MALT). The authors emphasize that immunophenotypic analysis is necessary (immunohistochemistry, flow cytometry, or molecular analysis by PCR) since a negative standard cytologic diagnosis does not entirely exclude PIOL.23 As PIOL is associated with a high incidence of CNS disease, to decrease intraocular surgery and attendant complications, CNS evaluation is important at the beginning including MRI and CSF cytology before examining ocular fluids and tissues.

Since between 56% and 85% of patients who initially present with PIOL eventually develop cerebral lesions, early diagnosis and appropriate treatment is imperative. Median time to diagnosis in a retrospective study from 16 centers in 7 countries was 6 months.24 Diagnosis was made by vitrectomy in 89%. Eleven % had positive CSF cytology. Of the 57% of patients who relapsed nearly half were in the brain alone and another 15% were in brain and eyes. PFS of 29.8 months and OS 58 months were similar to those of PCNSL without eye involvement. Investigational strategies include HA22, a hybrid protein of Pseudomonas exotoxin A linked to an anti–CD22 monoclonal antibody that interacts with the surface of lymphoma cells.

**CNS METASTASES**

**Epidemiology**

The majority of patients who develop CNS metastases do so at a time of advancing systemic disease. Exceptions to this scenario are primarily lung cancer patients up to 20% of whom may present with neurologic findings due to brain metastases before a primary cancer is identified. Thus, a cost–effective workup in patients who have an MRI appearance typical of CNS metastases but no known primary includes chest X Ray/chest CT and skin examination (melanoma) and no other extensive metastatic surveys are likely to be helpful.

Though the above tumors may cause neurologic problems early in the patients’ course, breast cancer is emerging as the most important systemic tumor with respect to
quality-of-life altering neurologic complications. As younger premenopausal patients are surviving longer with Her 2+ markers, the brain has become a sanctuary for metastatic disease. On average, breast cancer patients with CNS metastases are 5 years younger than those with disease metastatic to other sites. Only 2.5% of patients with initially localized disease ultimately develop CNS metastases whereas over 13% of those with stage IV disease develop metastases. The overall range of clinically evident breast cancer metastases is 10–16%. Several case examples of lung and breast cancer neurologic issues will be shown in the accompanying slides.

The major themes in breast cancer of which neurologists and neuro-ophthalmologists should be aware in order to interpret patient symptoms are:

1. Slightly increased stroke risk with anti-estrogen treatment (Tamoxifen)
2. Occult brain metastases incidence of 14.8% in clinical trial screening
3. Increased risk of carcinomatous meningitis after stereotactic radiosurgery (trastuzumab intrathecally is an emerging therapy)
4. Increasing responsiveness of brain metastases to chemotherapy (capecitabine and lapatinib)25

**NEURO-OPHTHALMOLOGIC ISSUES**

With new chemotherapeutic regimens have come new diseases. The reference by Li et al provides an excellent summary of drug-induced ocular disorders including many chemotherapy agents employed in both primary and systemic tumors.26 We will discuss two that have potential for neuro-ophthalmologic presentation:

1. **Capecitabine**, a drug that has promingly produced 3 complete responses (CR) and 3 stable disease (SD) out of 7 patients with CNS breast metastases with PFS 8 months and OS 13 months, has been reported to produce a multifocal leukoencephalopathy that looks much like multiple sclerosis.27

2. **RPLS (reversible posterior leukoencephalopathy syndrome) or PRES (posterior reversible encephalopathy syndrome)** is a clinical and radiological syndrome characterized by bilateral, reversible, often symmetric edema. The imaging findings are consistent with subcortical vasogenic edema prominently in the posterior temporo-occipital regions though the splenium, brainstem and cerebellum can be involved. The calcarine and paramedian occipital lobe structures are spared, helping to distinguish RLPS from posterior cerebral artery infarction and on diffusion weighted imaging as well as apparent diffusion coefficient mapping the edema is vasogenic. It develops acutely in patients with hypertensive encephalopathy, eclampsia and with a growing list of medications. It may present with prominent visual disturbance including cortical blindness with hypertension, confusion, and/or seizures. An increasing range of drugs has been implicated including: bevacizumab, sorafenib, l-asparaginase, G-CSF, erythropoietin, cisplatin, oxaliplatin, cyclophosphamide, tacrolimus, cyclosporine sirolimus and gemcitabine.28 Prognosis is excellent when the offending agent is withdrawn and hypertension is controlled. The differential diagnosis includes chemotherapy-related multifocal demyelination syndrome, radiation necrosis, metastases, stroke, venous thrombosis and, when the brainstem is involved, osmotic demyelination syndrome.29

**SURVIVING BRAIN TUMORS: THE COST OF TREATMENT—NEW THERAPIES, NEW CONSEQUENCES**

As more patients survive primary and systemic cancer, a host of new complications and, indeed, new diseases has emerged, many of which involve the central nervous system. In this lecture as well as in greater detail in the next, we will discuss the changing spectrum of infections after intensive chemotherapy, with particular attention to the often visually symptomatic progressive multifocal leukoencephalopathy30 and with the phenomenon of immune reconstitution mimicking tumor and presenting as a mass lesion.

For patients who have survived primary brain tumor treatment a host of long-term consequences threaten quality of life. These include cognitive decline and vascular disease from radiation therapy, progressive hearing loss from posterior fossa radiation, adrenal insufficiency and hypothalamic/pituitary dysfunction, communicating hydrocephalus, secondary neoplasms including meningiomas (median 20 years), sarcomas, thyroid cancers, basal cell carcinomas, and astrocytomas (median 8 years after treatment).

Two additional very recently described syndromes are of relevance to neuro-ophthalmologists as their initial symptoms may be visual:

1. **Superficial siderosis**: Patients who have had cerebellar tumor removal (usually medulloblastoma) and radiation develop late deterioration in hearing, sometimes new diplopia often new balance problems and almost always progressive cognitive decline. These patients have superficial siderosis or coating of the cerebellum and brainstem with hemosiderin visualized as a hypointense rim on T2 images with cavernous angioma (induced by radiation) detected on gradient echo sequences. The episodic bleeding from these cryptic vascular malformations leads to the deterioration and to a second problem.

2. **Stroke-like migrainous episodes after radiation therapy (SMART syndrome)**. Such patients, usually young or middle aged adult survivors of medulloblastoma develop prolonged visual or sensory
or hemiplegic auras lasting for days and succeeded by a headache, though the aura is more prominent.31

It is important that all physicians involved in neurologic diagnosis be aware of the evolving spectrum of diseases caused by our imperfect therapies. Brain tumor treatment has come some distance in the past thirty years, but more effective and less toxic therapies are needed. Until such treatments are found, both neurologists and neuro-ophthalmologists remain near the front lines of diagnosis and treatment that on a day to day basis can improve quality of life in CNS tumor survivors.

CME ANSWERS

1. B
2. C
3. E

REFERENCES

LEARNING OBJECTIVES
1. The audience shall have gained an understanding of paraneoplastic retinopathies and optic neuropathies.
2. The audience should have an understanding of a non-paraneoplastic autoimmune related retinopathy and optic neuropathy.
3. The audience should be able to distinguish between these entities and what treatment modalities may be available.

CME QUESTIONS
1. For patients with cancer-associated retinopathy, all of the following are true except one:
   a. They typically have a severely reduced ERG
   b. They usually display a marked loss of vision
   c. They often have photopsias
   d. Small cell carcinoma of the lung is one of the more common associated tumors
   e. The visual loss is easily treated with appropriate immunologic therapy
2. All of the following are true about melanoma-associated retinopathy except one:
   a. The ERG shows a markedly reduced B wave, with a normal A wave
   b. Flickering photopsias are common
   c. The treatment of MAR syndrome is never helpful
   d. The condition normally affects males
   e. Central vision acuity may be normal or show severe reduction
3. Patients with autoimmune related retinopathy and optic neuropathy (ARRON Syndrome) have all the following characteristics except one:
   a. May be responsive to steroid therapy
   b. May have other systemic autoimmune diseases
   c. May have an abnormal ERG as well as optic atrophy
   d. Can have a prolonged course of visual loss
   e. Their visual loss may be associated with cancer

KEY WORDS
1. AIR Syndrome
2. ARRON Syndrome
3. CAR Syndrome
4. DUMP Syndrome
5. MAR Syndrome
6. PON Syndrome

INTRODUCTION
This lecture will cover the following topics:
1. Terminology used for Autoimmune Retinopathy and Optic Neuropathy
2. Antiretinal Antibody Detection and Measurement
3. Cancer Associated Retinopathy (CAR Syndrome)
   a. Cancer Associated Cone Dysfunction (CAC Syndrome)
4. Paraneoplastic Optic Neuropathy (PON Syndrome)
5. Diffuse Uveal Melanacytic Proliferation (DUMP Syndrome)
6. Melanoma Associated Retinopathy (MAR Syndrome)
7. Autoimmune–related Retinopathy & Optic Neuropathy (ARRON Syndrome)
   a. Nonparaneoplastic Retinopathy with Cystoid Macular Edema (npAIR/CME = ARRON/CME)

1. Terminology
The terminology used to describe autoimmune retinopathy and optic neuropathy has been confusing. The confusion is related to the fact that the various autoimmune syndromes are not well defined in terms of specific immunologic and etiopathogenesis. We favor the terms used in the introduction above. In addition the terms AIR (Autoimmune retinopathy) has been used to describe patients with both cancer and non cancer. AIR is then subdivided into CAR Patients and nonparaneoplastic AIR (npAIR). There is a group of npAIR patients who have cystoid macular edema (npAIR/CME). Also the term AR (Autoimmune Retinopathy) has been used by Adamus to describe nonparaneoplastic autoimmune retinopathy patients. The problem with the terms both AIR and AR is that they do not consider that many of these syndromes...
may include optic nerve abnormalities with optic atrophy and antibodies to the optic nerve. Thus, we favor the term ARRON Syndrome (Autoimmune-related retinopathy and optic neuropathy). The term “autoimmune-related” is used rather than simply “autoimmune” because it is unclear whether, in all cases, the antibodies that are generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non-specific breakdown of retinal and optic nerve proteins. We now recognize from the work of Heckenlively that some cases of ARRON may have cystoid macular edema and we would call these ARRON with CME. ARRON/CME is discussed in much greater detail later in this lecture under ARRON Syndrome.

2. Antiretinal Antibody Detection and Measurement
Various autoimmune syndromes are not well defined in terms of immunologic and genetic abnormalities that define these syndromes. The more we learn about these autoimmune syndromes the more complex is the information discovered. We and others have found that the normal human serum contains many antibodies to retina and optic nerve. Forooghian et al has written of the need to standardize the detection and measurement of antiretinal antibodies. The authors discuss the use of Immunohistochemistry, Western blot, and Enzyme-Linked Immunosorbent Assay: ELISA in defining these syndromes. We agree completely with the concepts in the paper.

We have used serum from over 100 normal controls for comparison of patients with possible autoimmune syndromes evaluating antibodies against both retina and optic nerve. Adamus has established a clinical testing laboratory (Laboratory Improvement Amendments (CLIA) Certification) in 2005 for testing antiretinal antibody and anti-optic nerve autoantibody by Western blotting and immunohistochemistry. However, despite these advancements we agree with Forooghian understanding of these syndromes from an immunologic and probably genetic standpoint is still in its infancy. The need for standard assays and multicenter collaborations will be essential to our understanding and defining of these various syndromes. Western Blot Techniques (WB) using human tissue to study retina and optic nerve is ideal, but while some investigators have found fresh human tissue not hard to obtain, it has often been difficult in other laboratories to get fresh human retina and optic nerve. We have found pig optic nerve and retina works well and correlates well with human tissue using Western Blot Techniques. Others have found human tissue alongside mouse and bovine retinal tissue works well.

While we feel it is important to diagnose and treat these various syndromes using immunologic techniques, we realize that in the diagnosis of these various syndromes the clinician cannot use immunology alone. The clinical conditions must be strongly correlated to make the appropriate diagnosis. In addition to treat these various syndromes while ideally the clinician would like to see the antibody titer reduced, we recommend that clinical parameters (including visual acuity, visual fields, color vision, ERG, OCT, and sometimes VEP) are the key to monitoring all these syndromes.

3. CAR and CAC Syndromes
Cancer-associated retinopathy (CAR syndrome) describes a visual paraneoplastic disorder generally associated with small cell carcinoma of the lung, usually containing antibodies against retinal elements and causing both rod and cone dysfunction. Often associated with photopsias, visual loss occurs usually over months and frequently precedes the discovery of cancer. Clinical difficulties associated with cone dysfunction include photosensitivity, abnormal visual acuity, color vision abnormalities, central scotomas and an abnormal cone-mediated electroretinogram (ERG). Clinical problems associated with rod dysfunction include nyctalopia, prolonged dark adaptation, peripheral or ring scotomas and an abnormal rod-mediated ERG. CAR has been rarely reported to be slowly progressive.

Blindness as a remote effect of cancer was first recognized and described in 1976 by Sawyer et al, followed by Keltner, Roth and Chang, who presented the next report of paraneoplastic retinopathy at the 1981 Walsh Society Meeting, describing a patient with cancer-associated vision loss (Keltner JL, Roth AM and Chang RS, unpublished data, 1981). The authors proposed, in that presentation, the autoimmune theory of cancer-induced blindness based upon the patient’s response to steroids as well as the demonstrated anti-retinal antibodies seen primarily reacting against photoreceptor cells. These findings were subsequently published in 1983. They confirmed the work of Kornguth et al who demonstrated anti-retinal ganglion cell antibodies in patients with small cell carcinoma of the lung.

The isolation of the 23 kd CAR retinal antigen was first reported by Thirkill et al in 1987. The first recognition of the 23 kd antigen as the photoreceptor component recoverin was by Thirkill et al in 1992. In that article, Thirkill et al showed that the nucleic acid sequence of a cDNA cloned from the library of human retina exhibited 90% homology with that of the bovine counterpart.

Addressing the question of sensitization, Thirkill et al in 1993, 1996, and 1997 found intraperitoneal cultivation of small cell carcinoma induced expression of relevant cancer associated retinopathy antigens while others described the expression of recoverin in biopsies of small cell carcinomas from patients with CAR. Several examples of small cell carcinomas actively expressing recoverin have been described and are considered responsible for the induction of the autoimmune attack on the retina of patients with the 23 kd CAR Syndrome. If autoimmunity is responsible for the vision loss in CAR patients, this immunologic cancer connection represents the most likely trigger mechanism.
With respect to expression of retinal proteins by cancers, the gene for mouse recoverin protein 23 kd was assigned to the mouse chromosome 11, closely linked to Trp53. While the human recoverin gene was mapped to the human chromosome 17 by Murakami et al in 1992, it was shown by Freund et al and McGinnis et al to be localized at position 17p 13.1, a region containing a number of cancer–related loci. This suggests a possible mechanism for the aberrant expression of recoverin, which results in sensitization to this 23 kd photoreceptor component. McGinnis et al proposed a hypothesis for CAR retinopathy as a single mutational event that inactivates a copy of the p53 tumor suppressor gene which turns on the synthesis of a recoverin protein with the cell line becoming cancerous because of the tumor’s loss of the suppressor activity of the p53 protein. Thus, synthesis of the recoverin epitopes outside the eye accounts for production of circulating antibodies against recoverin which may inactivate recoverin with closure of the ion channels and depolarization of cells sufficient to kill the photoreceptors. McGinnis et al also felt that the event might be a deletion or the translocation with joining of the recoverin sequence to an active gene.

The underlying mechanism involved in the CAR syndrome, as in other paraneoplastic retinopathies, is probably related to molecular mimicry. According to this mechanism, paraneoplastic retinopathies occur when susceptible individuals produce immune response to a cancer antigen which cross reacts inappropriately with a retinal protein. Anti–recoverin antibodies appear to bind with the target molecules in the retina to cause apoptotic cell death. Anti–recoverin antibodies probably block the function of recoverin which regulates rhodopsin phosphorylation in a calcium–dependent manner. Certain cancers produce a recoverin protein aberrantly expressed in the cancer tissue which is recognized by the immune system of the patient. The secondary anti–recoverin antibody then reaches the retina and is taken into the photo receptor cell. It is felt that the antibody blocks the recovery function and enhancement of rhodopsin phosphorylation to induce the retinal apoptosis. Adamus et al have demonstrated that anti–recoverin induces an increase in intracellular calcium, leading to retinal cell death via a mitochondrial apoptotic pathway. In addition nifedipine has been found to protect against anti–recoverin induced apoptosis.

Retina proteins other than the 23 kd recoverin are implicated in the CAR syndrome, revealing a collection of potential autoantigens distributed throughout the neurosensory retina, with active counterparts in the brain. In our experience, the 23 kd recoverin protein is still the most common antigen linked with cancer–associated retinopathy. The next most common retinal antigen antibody reactions appear to be those involving a 40 kd protein followed by 45 kd and 60 kd proteins, non of which have been cloned to provide the exact protein sequence of the retinal antigen involved. It is relevant to note that over 20 antigens have been described in the CAR syndrome distributed throughout the retina (in rods, cones, ganglion cells and other various retinal components) and in the optic nerve. Table 1.

<table>
<thead>
<tr>
<th>Non 23Kda Paraneoplastic antigens to retina and/or optic nerve</th>
<th>Resources</th>
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<tbody>
<tr>
<td>24Kda</td>
<td>32</td>
</tr>
<tr>
<td>26Kda</td>
<td>77</td>
</tr>
<tr>
<td>34Kda</td>
<td>36</td>
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<tr>
<td>35Kda</td>
<td>187</td>
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<tr>
<td>40Kda</td>
<td>187</td>
</tr>
<tr>
<td>45Kda</td>
<td>28,128</td>
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<tr>
<td>46Kda (Anti-enolase)</td>
<td>31,64,65</td>
</tr>
<tr>
<td>48Kda</td>
<td>25,32</td>
</tr>
<tr>
<td>50Kda</td>
<td>20</td>
</tr>
<tr>
<td>60Kda</td>
<td>38</td>
</tr>
<tr>
<td>62Kda (CRMP-5)</td>
<td>37,81,85</td>
</tr>
<tr>
<td>65Kda</td>
<td>21</td>
</tr>
<tr>
<td>70Kda</td>
<td>21</td>
</tr>
<tr>
<td>Anti-ganglion cell antibodies and anti-neurofilament (70Kd, 145Kd, 205Kd)</td>
<td>10,14,15</td>
</tr>
<tr>
<td>Anti-hsc70</td>
<td>189,190</td>
</tr>
<tr>
<td>TULP1- (Tubby-like protein)</td>
<td>75,191</td>
</tr>
<tr>
<td>PRN (Photoreceptor cell-specific nuclear receptor gene product)</td>
<td>192-194</td>
</tr>
<tr>
<td>PTB</td>
<td>195</td>
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</tbody>
</table>

Ohguro reported that aberrant expression of recoverin was identified in more than 50% of tumor cells from several types of cancer including gastric, lung and other cancers. Their data showed that recoverin–expressing cancer cells induced tumor immunity and provided a favorable prognosis for primary cancer in CAR patients.

Peek has reported that in two CAR patients the 40 kd protein was located to the photoreceptors and a 35 kd protein was located in the outer plexiform layer.

Misiuk–Hojo reported in a screening of 295 patients with diagnosed breast cancer that 6 out of 295 patients (2%) had high–titeres of antibodies to retinal antigens. These patients underwent an ophthalmic and neurologic exam and 2 were found to have symptoms of CAR.

Querques reported the third case of CAR associated with invasive thymoma and first case reported with antibodies to a 145 kd protein believed to interphotoreceptor retinoid–binding protein (IRPB) and choroidal neovascularization.
Retinal enolase, the 46 kd protein, has also been associated with CAR syndrome.\textsuperscript{31,64-65} However, Gitlits et al\textsuperscript{66} reported the presence of enolase in a patient with discoid lupus erythematosus and showed enolase autoantibodies in two patients without systemic disease, suggesting that enolase autoantibodies have a broad association and are not restricted to any particular disease.

There are numerous types of malignancies associated with CAR. The most common cause for CAR syndrome is small cell carcinoma of the lung. The next most common is uterine cancer including endometrial and cervical cancer. They are followed by lymphoma, prostate cancer, laryngeal cancer, colon cancer, pancreatic cancer, undiagnosed cancers and metastatic cancers from unknown cause.

Treatment modalities used in the CAR syndrome as well as non–CAR autoimmune retinopathy and optic neuropathy include:\textsuperscript{9-43,67} 1) treatment of the underlying primary cancer; 2) prednisone; 3) plasmapheresis; and 4) intravenous immunoglobulin (IVIg).\textsuperscript{1,48} Monitoring anti–retina titers in response to immunomodulation can prove useful in patient management.\textsuperscript{1,12,21,38,66} Monitoring antibody titers demonstrates whether immunosuppressant therapy is controlling the autoimmune process. If a titer does not fall to baseline level, other immunosuppressant measures may be necessary. There is concern that reducing the antibody response could increase cancer mortality, however, we are unaware of any documented example. However, monitoring anti–retinal titers may not be practical. Thus, it becomes necessary to following as many objective parameters of visual function as possible to tell if visual loss has stabilized. Visual acuity, visual fields and color vision are the easiest to follow. Also, ERG and sometimes VEP may be helpful. Mohamed reported OCT findings in a CAR patient.\textsuperscript{69} Patients need to know that their vision may not improve and if the visual loss can be stabilized that is success in treating CAR syndrome.

Treatment efforts have had variable outcomes presumably because once photoreceptors or other retinal structures are irreparably damaged, immunosuppressive therapy will not work. There have reported patients with CAR syndrome who have improved with treatment\textsuperscript{11,38,67-68} and those who despite plasmapheresis, had no improvement.\textsuperscript{21} Guy and Aptsiauri have reported on 3 patients with CAR treated with IVlg. One demonstrated improvement in acuity and visual field, another showed improvement in visual field and the third stabilized.\textsuperscript{68} Espandar et al reported a patient with CAR who responded to alemtuzumab (Campath) a monoclonal antibody against the cell surface glycoprotein CDf2 expressed in B and T lymphocytes, monocytes and macrophages. This patient had been treated with plasma exchange and cyclosporine treatment and had not improved. Over an eight year period the patient had many episodes of recurring retinopathy which improved with each alemtuzumab treatment. Further studies will need to be done to see if this treatment works in other cases.\textsuperscript{70} It appears that while much information on autoimmune retinopathies can be obtained from the study of CAR and MAR patients, the possibility that comparable immunologic reactions may develop in unrelated retinopathies must also be considered. Systemic autoimmune diseases such as lupus and rheumatoid arthritis must be considered potential causes for autoimmune retinopathy. Inherited retinal degenerations, and those of unknown cause, must also be examined for similar indications of immunologic involve, since the dissolution of the retina may lead to abnormal reactivity to any or all of the recognized autoantigens, such as the S–antigen, the interphotoreceptor retinoid–binding protein (IRBP) and rhodopsin.\textsuperscript{71-73}

The recent upsurge of interest into the immunologic aspects of vision loss in non–cancer patients\textsuperscript{38,71} and cancer patients\textsuperscript{74-77} supports evidence of autoimmune involvement in associated retinopathies. Recent presentations by Heckenlively et al\textsuperscript{71} and Aptsiauri et al\textsuperscript{73}, demonstrated patients with progressive panretinal degeneration from such conditions as idiopathic retinopathies and retinitis pigmentosa who had CAR–like clinical changes in association with the presence of antibodies to recoverin and other retinal proteins. Further research into this group of cancer–related and non–cancer–related retinopathies may lead to basic understandings of visual loss associated with a variety of retinal degenerations.

The diagnosis of CAR syndrome cannot be made by testing for a single antigen. More extensive immunologic testing is necessary. Thus, appropriate clinical history, physical and ophthalmologic examination, laboratory examination, electrophysiologic findings, and immunologic testing are necessary to diagnose the CAR syndrome and separate it from other non–cancer–associated autoimmune retinopathies. It is important to appreciate that cancer–associated retinopathy and recoverin–associated retinopathy may be related entities, the understanding of which is currently evolving.

Cancer Associated Cone Dysfunction (CAC Syndrome) is a subset of CAR Syndrome wherein antibodies are primarily directed against cones. By contrast, CAC patients have photophobia, loss of color perception, central scotomas, and an ERG showing a reduction in the cone responses. Cogan described the first case of this in 1990.\textsuperscript{21} An unusual case of cone dysfunction was described by Jacobson and Thirkill with the presence of 23Kd and 50Kd antibodies.\textsuperscript{78} Campo et al, described a small cell carcinoma of the endometrium with an ERG showing decreased cone response.\textsuperscript{79} Parc reported a 50 year–old woman with CAC and abnormalities restricted to cone dysfunction with laryngeal carcinoma. The serum from this patient had two retinal antigens approximating 40 Kd that localized to the outer segments of the photoreceptor layer.\textsuperscript{80}
4. Paraneoplastic Optic Neuropathy

Paraneoplastic Optic Neuropathy is a rare syndrome less commonly diagnosed than the CAR syndrome. However, to completely separate them is probably incorrect since it is known that there may be antigens which cross-link both in the optic nerve and retina. Paraneoplastic optic neuropathy is a subacute, progressive, frequently bilateral painless loss of vision, however it can present with acute visual loss. The important diagnosis to eliminate is that the patient does not have direct compression or infiltration of the optic nerve. Pathologic findings have shown non-specific vascular infiltration by lymphocytes as well as delimitation of the axons. Associated findings in patients with PON include cranial nerve palsies, polyneuropathy, vertical or down-beating nystagmus, as well as cerebellar signs.

Paraneoplastic optic neuropathy can also be associated with a subacute cerebellar syndrome. Most of these patients have a serum antibody specific for a recently defined 62 Kd neuronal antigen named collapsing response-mediating protein-5 (CRMP-5). Yu et al., described the paraneoplastic IgG autoantibody, a neuronal cytoplasmatic protein, a previously unknown 62 Kd member of the CRMP family. Since 1993 they have seen 121 cases in their laboratory. They believe that CRMP-5 is as frequent as PCA-1 (anti-Yo) autoantibody, and second in frequency only to ANNA-1 (anti-Hu). Other neurological signs revealed in clinical information of 116 patients were high frequencies of chorea (11%) and cranial neuropathy (17%, which includes 10% loss of olfaction/taste, and 7% optic neuropathy). Additional common signs were peripheral neuropathy (47%), autonomic neuropathy (31%), cerebellar ataxia (26%), subacute dementia (25%), and neuromuscular junction disorders (12%). Spinal fluid was inflammatory in 86%. In 37% of cases, the level of spinal fluid CRMP-5 IgG either equaled or significantly exceeded serum titers. Lung carcinoma (mostly limited small-cell) was discovered in 77%, thymoma in 6%. Half of the remaining patients had miscellaneous neoplasms (all but two were smokers). In all cases, serum IgG bound to CRMP-5 (mostly N-terminal epitopes), but not to human CRMP-2 or -3. Yu et al., have proposed that in all likelihood, the anti-CV2 autoantibody is CRMP-5 specific.

Dr. Shelly Cross presented at NANOS a subset of patients with CRMP-5 IgG. 172 patients presented with subacute neurologic disorders. Fifteen patients had optic neuritis with retinitis documented in five. The fifteen optic neuritis patients were age 52–74 and were smokers; 8 were female. Fourteen had subacute visual loss and field defects. Four out of 4 tested had abnormal ERGs; vitreous cells were seen in nine. Two patients with myelopathy and optic neuritis bore a superficial resemblance to Devic’s disease. Other neurologic abnormalities included change in mental status, cranial neuropathies, movement disorders, myelopathy, peripheral nerve disorders, cerebellar and autonomic dysfunction. Small-cell lung carcinoma was confirmed in 10 patients, the remaining 5 had another carcinoma or provisional evidence for lung cancer. CRMP-5 IgG was detected at 1:1,000 to 1:500,000 dilution. No serum had CAR-IgG. Vitrectomy revealed reactive lymphocytosis (4/4) (the one case test was predominantly CD4+). Western blots demonstrated full-length CRMP-5 protein in optic nerve retina. Peroxidase staining revealed cytoplasmic immunoreactivity in retinal ganglion cells, nerve fiber layer and photoreceptor cells. Thus, Dr. Cross and associates have identified CRMP-5-IgG, a novel paraneoplastic ophthalmic process of combined optic neuritis and retinitis accompanied by vitreal inflammation. Margolin reported on CRMP-5 PON and vitritis as the only clinical manifestation in a patient with small cell lung carcinoma.

Isolated cases of PON without other CNS pathology are rare. There appear to be only four cases of isolated CRMP-5 reported. There appears to be only two cases of CRMP-5 PON to report neuropathologic findings.

We recently had a case of isolated PON with breast cancer with a 22Kd protein against both optic nerve and retina and no evidence of CRMP-5. She was diagnosed with breast cancer and had a remote history of lung and cervical cancer. The patient while initially responding to treatment for her visual loss eventually had progressive visual loss and died of her breast cancer.

Bilateral optic neuropathy and subacute ataxia were manifestations of a paraneoplastic neurologic disorder in a woman found to have a small cell carcinoma of the lung. Serologic tests revealed a neuronal autoantibody specific for CRMP-5, a 62 Kd member of the collapsing response-mediating protein family. Unexplained optic neuropathy in the setting of subacute cerebellar ataxia should cause suspicion of a paraneoplastic disorder and prompt testing for this autoantibody, especially in patients at risk for lung carcinoma. Treatment of paraneoplastic optic neuropathy results have been highly variable but can result in visual improvement.

5. Diffuse Uveal Melanocytic Proliferation (DUMP Syndrome)

What has been called the bilateral diffuse uveal melanocytic proliferation (DUMP) syndromes characterized by bilateral progressive cataracts, iris masses, choroidal melanocytic proliferation, and overlying detachment associated with a cancer. This is a rare disorder with associated ocular features which include: round or oval, subtle red patches at the level of the retinal pigmented epithelium in the posterior fundus with early hyperfluorescence on fluorescein angiogram corresponding to these patches; multiple, slightly elevated pigmented and non-pigmented uveal melanocytic tumors involving the iris; diffuse thickening of the uveal tract; exudative retinal detachment; and rapidly progressive cataracts. This is generally associated with a systemic cancer which may not be recognized at the time of the ocular symptoms. This usual progresses in a rapidly fatal fashion.

Approximately 25 cases have been reported in the literature, with 23 involving malignant tumors. The average survival from initial presentation was 16.8 months. Three patients survived without recurrence for...
of reported cases is difficult to determine. We have serum documented; 11 cases are described here for the first time. In this report, we add the features of these 11 cases to the 51 cases previously reported. In our report of 62 MAR patients there were 33 men and 7 women (4.7 to 1 men over women). The age of onset was averaged 57.5 years (range 30 to 78 years). Visual acuity of 20/60 or better was initially present in 82% of the cases. Fundus examination was normal 44%, optic disc pallor 23% and retinal vessel attenuation was present 30%. Vitreous cells were present in 30%.

While in our series the fundus was usually normal except for optic pallor, several other investigators have reported a variety of fundus findings. Borkowski et al reported 2 patients, one patient with an oval shaped white lesion in the outer retina and patient 2 with well-circumscribed chorioretinal atrophic lesions, (note the fundus had been normal 4 years earlier). Patient 2 developed vitiligo with onset of the new metastases and the fundus lesions. Zacks reported a 69 year old with recurrent exudative retinal detachments with a history or a choroidal melanoma 23 years earlier. Palmowski et al reported a 33 year old female with MAR Syndrome with disabling glare and an RPE detachments with small yellow-orange lesions. Treatment of the metastatic melanoma with removal of the metastasis and chemotherapy resulted in regression of the RPE detachment and resolution of the orange material. Biancietto et al also reported multiple RPE detachments of the neurosensory retina with antibodies to interphotoreceptor retinal binding protein (IPBP).

The earliest report of a patient with MAR–like syndrome is credited to Gass in 1984, the patient, who had profound visual loss together with a diagnosis of metastatic melanoma, was believed to have an acute Vogt–Koyanagi–Harada–like syndrome. Vision improved dramatically following steroid treatment, a response very different from subsequently reported MAR cases. The patient also had a prominent vitreous and anterior chamber cellular reaction, lymphocytic cerebrospinal fluid pleocytosis, and depigmentation of the retina and skin. These signs suggest an uveomeningitic syndrome rather than MAR syndrome.

Two more cases of patients with a MAR–like syndrome were described prior to the recognition of MAR as a distinct clinical entity. The first, reported by Ripps et al in 1984, was attributed to vincristine toxicity. The second, reported by DuBois et al. in 1988, initially attributed night blindness to migraine. In 1991, the same authors reported in a letter that the patient had developed cutaneous malignant melanoma two years after the onset of night blindness, and acknowledged the similarities between their case and a case of MAR reported in 1988 by Berson and Lessell.

The seminal paper on MAR syndrome, by Berson and Lessell, postulated a paraneoplastic cause of night blindness in a patient with malignant melanoma. Subsequently, Milam et al recognized that patients with MAR have circulating IgG autoantibodies showing specific immunofluorescent staining of some human rod bipolar cells.
The bipolar cell antigens upon which these antibodies react remain unknown; some evidence suggests that they are made of polar lipid.\textsuperscript{125}

MAR syndrome affects predominantly males. The male-to-female ratio of 4.7:1 far exceeds the 5:4 incidence of malignant cutaneous melanoma in the United States.\textsuperscript{157} MAR patients have been believed to retain near-normal visual acuity, color vision and central visual field\textsuperscript{40}, but our review clearly shows that some lose central vision. Visual acuity may deteriorate later on, showing central and peripheral loss with progression.

Visual symptoms include shimmering, flickering, or pulsating photopsias and difficulty with night vision. The ERG shows the typical features of a markedly reduced dark–adapted b-wave, and preservation of a-wave, resembling that seen in CSNB.\textsuperscript{40} Defects in the function of cones “ON”–center bipolar cells and blue–sensitive cones occur in some patients.\textsuperscript{131–136} There is evidence that the damage is restricted to cells of the magnocellular pathway.\textsuperscript{130} The “Off” or hyperpolarizing, bipolar cells are said to be spared.\textsuperscript{131, 136} Other abnormal electrophysiologic findings reported in some MAR patients are reduced a-wave amplitude in the photopic or scotopic ERG\textsuperscript{133, 143}, reduced amplitudes of the photopic ERG\textsuperscript{131, 133, 136–137}, reduced amplitudes of oscillatory potentials\textsuperscript{131–134}, maximum stimulus intensity amplitude reduction\textsuperscript{136}, abnormalities in the 30Hz–flicker response latency\textsuperscript{132–133, 138, 141} or amplitude\textsuperscript{133, 136}, and an abnormal pattern–ERG.\textsuperscript{145} Alexander reported in two patients with MAR that the contrast sensitivity loss is not specific to the magnocellular pathway, but related to the spatial frequency of the test target and consistent with the dysfunction of the bipolar cell layer.\textsuperscript{158} Kim et al reported a case of MAR Syndrome with spontaneous improvement of the rod system function.\textsuperscript{159}

In our study, two patients showed an almost extinguished ERG pattern with diffuse loss of both a-wave and b-wave. One patient had an abnormal ERG in only one eye.\textsuperscript{55}

The MAR syndrome is generally believed to occur only after patients have developed metastatic melanoma.\textsuperscript{125} Our review however, disclosed two patients who presented with MAR before the diagnosis of a primary melanoma, three who had no evidence of metastatic disease, five who presented with a simultaneous diagnosis of metastatic cutaneous melanoma and MAR, and six whose metastasis was diagnosed after the onset of MAR. In addition, one case of MAR-like syndrome has been described in a patient with antiretinal bipolar cell antibodies with no cutaneous melanoma after 4 years of follow up.\textsuperscript{160}

The immunologic and electrophysiologic abnormalities in patients with MAR syndrome suggest that the underlying pathogenic mechanism is molecular mimicry, such as has been described in other paraneoplastic syndromes.\textsuperscript{56} According to this mechanism, MAR syndrome occurs when susceptible individuals produce an immune response that cross-reacts with retinal rod bipolar cells, with which the melanoma cells share antigenic epitopes. Neuroretinal transmission from the photoreceptors through the inner retina is then disrupted.\textsuperscript{125, 132} Our finding that the metastatic melanoma removed from patient 58 expressed antigens that react with rabbit anti–whole bovine retina antibodies supports the proposal of molecular mimicry as the underlying pathogenic mechanism in MAR syndrome.

Immunologic heterogeneity is recognized in MAR. Involvement of “ON” bipolar cells has been implicated.\textsuperscript{125, 131, 142} We previously reported that one patient had an autoantibody reaction with a 22–kDa neuronal antigen found in the retina, but not in the optic nerve.\textsuperscript{161} Other studies have suggested that a novel membrane– associated 33–kDa protein and a 35–kDa retinal Muller cell protein could be the MAR antigens.\textsuperscript{144, 162} In our study, the variety of retinal antigens involved in indirect immunohistochemical staining and Western blot analysis strongly suggests that several antigens, shared by the retina and the neoplasm, may be involved. In addition, anti–bipolar cell antibodies have been demonstrated in a patient with CAR syndrome from adenocarcinoma of the colon.\textsuperscript{163} Transducin was demonstrated in a patient with MAR syndrome.\textsuperscript{164}

Although our patients’ sera specifically recognized retinal bipolar cells with indirect immunohistochemistry, we were unable to identify MAR–specific retinal antigens by Western blot technique. It has been postulated that the absence of specific staining by MAR sera on Western blots could be due to modification of amino groups by paraformaldehyde, denaturation by sodium dodecyl sulfate, and obscuration of MAR–specific antigen by a nonspecifically stained component.\textsuperscript{132} It is possible that the MAR–specific retinal antigens may not be proteins, but gangliosides, proteoglycans\textsuperscript{132}, lipids\textsuperscript{125}, carbohydrates, or a combination of these substances. Brazhin et al they developed a murine model for MAR in ret–transgenic mice. They found arrestin and transducin in MAR patients. Adoptive transfer of splenocytes from tumor–bearing wild-type mice led to induction of retinopathy in 4/16 mice. This suggests that MAR can be mediated by humoral and/or cellular immune response against a number of CAR antigens which may function as paraneoplastic antigens in MAR.\textsuperscript{165} In addition they demonstrated for the first time to different autoantibodies against two different cancer related proteins in the same MAR patient. These antibodies were against arrestin and transducin.\textsuperscript{165–166} They feel that MAR syndrome is likely induced by an immune response against multiple retinal antigens\textsuperscript{166–167}.

Milam et al reported that sera from MAR patients and some normal subjects produced nonspecific background labeling of all parts of the human retina and specific staining of nerve fiber layer.\textsuperscript{132} A pattern of diffuse staining of human MAR IgG throughout the retina in rhesus monkey eyes was recently reported.\textsuperscript{142} We found that the analysis of MAR sera by indirect immunohistochemistry on sectioned rhesus monkey eyes disclosed diffuse antibody involvement with optic nerve, retinal nerve fiber layer and photoreceptors, as well as bipolar cells. Notably, over half of the UC Davis patients
showed optic disc pallor. The staining of nerve fiber layer, optic nerve and ganglion cells may be related to damaged neurotransmission or merely a harmless epiphenomenon.

Recently other authors have found the melanoma-associated retinopathy may be related to a variety of anti-retinal antibodies, as we discussed in our article. Potter et al found recognition of a transducin, a novel melanoma-associated retinopathy antigen which may be important when identified by Western blot. They found no immunoactivity against bipolar cells by immunohistochemistry.

Ladewig reported on the screening of 77 serum samples with 51 patients with different stages (Am Joint Committee on Melanoma Cancer Stages I–IV). Of the 77 samples 53 (69%) were found to have antibodies reactive with various components of retina. Statistical analysis revealed a correlation between antibody activity and the stage of the disease with the higher percentage of antibody activity in advanced stages of melanoma. None of the patients had symptoms of MAR. Follow-up studies of these patients will be needed to see if any develop MAR and the significance of these findings. Pfohler has reported on the high frequency of subclinical findings of MAR in patients with melanoma. No follow-up to these 53 patients with antibodies reactive with various components of the retina has been published. However, I have had a personal communication with Claudia Phohler in October 2009 and she relates to me that of the 49 patients followed since their original papers, only one patient developed MAR Syndrome. The MAR Syndrome resolved with treatment of the melanoma. None of the other 49 patients who had retinal antibodies developed MAR Syndrome. Pfohler has also reported that antiretinal antibodies are not always associated with prolonged survival in melanoma patients.

Histopathologic studies of postmortem retinas from MAR patients have been previously reported. In the first case, Okel et al found considerable loss of macular anatomy, with marked degeneration of photoreceptor cells and extensive destruction of the neurosensory retina beyond the bipolar layer. In the second case, Gittinger and Smith observed marked reduction in the density of bipolar neurons in the inner nuclear layer. Photoreceptor cell nuclei in the outer nuclear layer were normal. Ganglion cells were present, although many showed evidence of trans-synaptic atrophy. These anatomical changes are consistent with the clinical, immunologic and electrophysiologic data that implicate the bipolar cells as the primary site in MAR syndrome. By contrast, in one patient whose eyes were made available for our study, histopathologic examination revealed no apparent anatomical abnormalities by light microscopy, even though indirect immunohistochemistry showed strong antibody activity upon nerve fiber layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer segment of photoreceptor cells, and the retinal pigment epithelium. Thus, the 3 cases of histopathology discussed above (two previously reported cases and the current study) showed the diverse findings of normal retinal structure to widely destroyed retinal structure. New information has been reported by Bazhin about the histology in MAR. Bazhin et al demonstrated in their murine model for MAR in ret-transgenic mice that melanoma-bearing mice showed similar signs of retina degeneration as reported in some patients with MAR. Specifically they found degeneration of photoreceptors, bipolar cells and pigment epithelium. This suggests that not only proteins of bipolar cells, but also photoreceptor proteins and possibly proteins of pigment epithelium could function as paraneoplastic antigens in MAR.

Recently Janaky identified what appeared to be a classic case of MAR Syndrome. The patient had classic MAR Syndrome in the right eye with typical ERG changes in field loss, while the left eye had normal vision and fields. It may be the first case report of a unilateral MAR Syndrome that after 18 months failed to spread to the second eye.

Treatment of the visual loss of MAR has often been ineffective. Occasionally combinations of cytoreductive surgery, x-irradiation, intravenous corticosteroids, plasma exchange, and IVIg have shown some benefit. Others have also found similar results with IVIG in case of MAR Syndrome.

IVIg has been shown to be efficacious in the treatment of two of three patients with paraneoplastic visual loss associated with CAR Syndrome. It has been useful in other autoimmune neurologic diseases, including Guillain–Barre Syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, multiple sclerosis, dermatomyositis, and in other immunologic ophthalmologic conditions, such as ocular cicatricial pemphigoid, refractory uveitis eye.

All preparations of IVIg are comparable in safety, efficacy and cost. While the different pools of human donors used by the various manufacturers contain a wide range of anti-idiotypic antibody specificities there are no documented differences in the efficacy of certain products or lots for a given patient or a specific disease. The empirical therapeutic dose of IVIg is 2g/kg. While the past practice has been to divide the total dose for infusion into 5 daily doses of 400 mg/kg each, the current recommendation is to divide the total dose into 2 daily doses of 1g/kg each. The rate of infusion should not exceed 200 ml/h or 0.08 ml/kg/min. Because of the drug’s rapid diffusion to the extravascular space, achieving a high concentration of IVIg within 2 days may enhance its efficacy.

There is concern that immunomodulatory therapy such as IVIg, while decreasing the titer of circulating autoantibodies, may increase the cancer mortality because MAR patients may have antibodies that are protective against tumor spread. However, in the patients whom we studied, there is no difference in survival between MAR patients, treated or untreated, and those without MAR. There are three experimental studies that show the efficacy of IVIg as an anti-tumor agent.
Current research suggests that cytoreductive surgery (complete metastasectomy) and adjuvant immunotherapy should be the initial treatment for most patients with melanoma metastatic to distant sites, since 90% of such patients have only one to three metastatic sites detectable with modern scanning technologies. Adjuvant immunotherapy can be used after the induction of a complete clinical remission by cytoreductive surgery. In a recent case of CAR Syndrome secondary to adenocarcinoma of the colon with retinal anti–bipolar cell antibodies, the ERG and visual fields were markedly improved after such therapy. Thus, effective treatment of cancer may result in elimination of associated anti–retinal antibodies and improved retinal function.

Cancer cells, including those of malignant melanoma, generate factors that facilitate tumor growth by suppressing the immune system. The degree of general immunosuppression correlates with the total burden of melanoma cells in the body. Melanoma cells also express multiple melanoma–associated antigens that may induce the production of circulating autoantibodies or other factors that block the ability of lymphocytes to kill melanoma cells, or activate T cells to suppress the anti–tumor response. These autoantibodies may cross-react with retinal rod bipolar cells in susceptible hosts, resulting in MAR Syndrome. Therefore, by removing most of the immunogenic activities of melanoma cells and decreasing the tumor burden, cytoreductive surgery not only facilitates the resolution of MAR, but also allows the recovery of the host’s anti–tumor immune response.

In our series among the 7 MAR patients who experienced visual improvement, 4 had cytoreductive surgery. Two patients improved with cytoreductive surgery alone, and two others received cytoreductive surgery in addition to IVIg. The importance of decreasing melanoma tumor burden in treatment of MAR Syndrome is further demonstrated by one particular patient’s clinical course. This individual experienced a worsening of visual acuity every time the metastasis recurred and improvement in visual acuity when the metastatic disease was reduced with radiation therapy. In MAR, as well as other CNS paraneoplastic syndromes, other therapies have been generally less effective than cytoreductive surgery and IVIg.

Results of a randomized trial in the adjuvant treatment of metastatic malignant melanoma have shown promise. Patients receiving adjuvant immunotherapies such as CancerVax/BCG and GM2 ganglioside/BCG vaccine had prolonged disease–free intervals and increased survival rate compared to those who received BCG alone. Vaccination with treated autologous cells has been attempted. Another emerging therapy involves the transfection of cutaneous malignant melanoma nodules with retrovirus–mediated herpes simplex type 1 thymidine kinase suicide genes, rendering the transfected cells susceptible to ganciclovir. In another study, autologous tumor cells transfected with IL–2 genes were injected back into patients to generate an immune response. Yet another approach involves injection of vaccinia/GM–CSF constructs directly into subcutaneous metastases.

The treatment of patients with malignant melanoma and MAR syndrome should be directed at decreasing the tumor burden, with resection of visible metastatic tumor masses by cytoreductive surgery so that any adjuvant immunotherapy can become more effective. Other medical treatments are reserved for patients whose ophthalmic manifestations are not relieved by these approaches.

7. Autoimmune–Related Retinopathy and Optic Neuropathy (ARRON) Syndrome (Not Associated with Cancer)

Patients with autoimmune–related retinopathy and optic neuropathy (ARRON) syndromes may often go unrecognized, and may be more common than either CAR or MAR syndromes. Although definitions of ARRON syndrome may evolve to include additional forms of vision loss, our experience with this syndrome has led us to describe it as a diverse group of patients, without malignancy, who produce antibodies that are reactive with the optic nerve an/or retina; and who may be responsive to steroid treatment or other immunomodulators. Those patients who do not initially exhibit abnormal antibody activity may later do so as their vision loss progresses. It is also possible that patients may experience immunologic abnormalities that are not detected by the methods described in this report.

The term “autoimmune–related” is used rather than simply “autoimmune” because it is unclear whether, in all cases, the antibodies that are generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non–specific breakdown of retinal and optic nerve proteins. We believe that many of these antibody reactions are related since immunologic treatment seems to help some of these patients. There are a variety of autoimmune reactions throughout the retina, choroid plexus, optic nerve, and blood vessels of the retina and optic nerve.

We have reported on a group of ARRON patients. We found the syndrome more commonly in women than men, the average age being 50. The visual loss was often asymmetric with visual acuity varying from 20/20 to no light perception. Eleven of 12 patients had optic neuropathy with ERG abnormalities present in 10 out of 11. Eight out of 12 patients had other systemic autoimmune diseases. Varieties of treatments have been tried with variable success and are generally based on standard therapy for other systemic diseases, which include: prednisone, IVMP, immunosuppressive therapy, plasma exchange and IVIg.
neuropathy. These patients generally had an acute to subacute onset rather than the chronic course of visual loss that many of our ARRON patients have demonstrated. Rush et al.\(^{218}\) reported on patients with a positive ANA and benign monoclonal immunoglobulin G (IgG) band, who developed an optic neuropathy that was responsive to corticosteroids. Dutton et al.\(^{219}\) described three patients with lupus-like syndromes and positive ANAs who presented with retrobulbar optic neuritis. Their vision improved with pulse IVMP acutely and was maintained with continued administration of prednisone and other immunosuppressives. The authors stress the importance of differentiating autoimmune optic neuropathy vs. multiple sclerosis. Patients with optic neuropathy of an autoimmune origin may become irreversibly blind if untreated, but patients with multiple sclerosis commonly recover spontaneously. They also bring attention to the early use of intensive steroid therapy, as they believe that is what led to good visual results in three of the four eyes in their study.

Jabs et al.\(^{220}\) reported seven women with SLE who presented with optic neuropathy. The authors state the importance of considering the possibility of SLE in young women who present with unilateral or bilateral optic neuropathy. Corticosteroid therapy improved the vision in four of their seven patients. Kupersmith et al.\(^{221}\) included a case series of 14 patients. Nine patients had bilateral optic neuropathy. Four patients started with a unilateral optic neuropathy, but involvement of the other eye developed from 1 to 17 years later. These patients lacked clinical signs of systemic collagen vascular disease, but they had blood abnormalities such as positive ANA (11 of 14 patients), or less consistently, positive Raji (1 of 3 patients evaluated) or anticardiolipin antibodies (4 of 5 patients evaluated). Skin biopsies in six of the seven patients evaluated showed IgG, IgA, IgM, or C3 deposits. The results of the treatment were remarkable. Eleven patients had dramatic improvement of vision with megadose intravenous corticosteroid therapy, nine of whom had previously failed to benefit from conventional doses of oral prednisone. Immunosuppressive therapy was later used to supplement corticosteroid therapy in maintaining vision. Their goal was to determine the lowest effective dose or to eventually eliminate corticosteroid entirely.

Riedel et al.\(^{222}\) reported two cases of steroid-responsive optic neuropathy following periods of immunosuppressive therapy over the years. Both patients had C3 and IgM deposition perivascularly and at the dermo–epidermal junction on skin biopsy. The diagnosis of autoimmune optic neuropathy was made on the presence of the immune complex deposition. Both patients responded to IVMP followed by oral prednisone use. Both were slowly tapered off corticosteroids after stabilization of their vision.

Frohman et al.\(^{223}\) reported a 12-year old patient with steroid-dependent optic neuropathy who experienced recurrent episodes of optic neuritis during multiple attempts at tapering the steroids. The patient’s serum was assayed and did not contain circulating antibodies against the optic nerve and retina. He was found to have a dysgammaglobulinemia, with decreased levels of IgG subclasses 2 and 3. Due to the long-term prednisone use, the patient experienced complications including growth delay and cushingoid features. However, with the initiation of a monthly regimen of IVIg, he was successfully tapered off the steroids without any complications or recurrence of visual symptoms.

These earlier reports by Rush et al.\(^{218}\), Dutton et al.\(^{219}\), Jabs et al.\(^{220}\), Kupersmith et al.\(^{221}\), Reidel et al.\(^{222}\) and Frohman et al.\(^{223}\) described patients with steroid-responsive optic neuropathy who probably had an autoimmune optic neuropathy. These early cases of steroid-responsive optic neuropathy may well have been cases we would now consider ARRON syndrome. However, available laboratory techniques at the time did not allow for detection of antibodies against the optic nerve and retina. Additionally, it is important to remember that antibodies may not always be detected secondary to immunosuppressive therapy or normal sampling serum variation. Alternatively, antibodies may be present but undetectable by current laboratory techniques. Multiple, serial antibody testing may be necessary to follow the course of a patient’s disease or response to treatment.

More recent reports that we would include in the ARRON syndrome include Mizener et al.\(^{224}\), Whitcup et al.\(^{225}\), Peek et al.\(^{226}\), and Keltner et al.\(^{161}\). These studies included patients with antibodies to various layers of the retina and optic nerve in the absence of cancer. Mizener et al.\(^{224}\) described two patients with anti-retinal antibodies that reacted with the inner plexiform layer of the retina. Both patients had severe monocular visual loss with photopsias, ring scotomas, and abnormal ERGs despite normal appearing fundi. They both had family and personal history of autoimmune disease. The evaluation for cancer in these patients was negative. Similar to patients described by Mizener, the patients in this study also had asymmetrical visual loss. Although the two patients in Mizener et al.‘s study\(^{224}\) both had photopsias, our group of ARRON patients seems to lack the photopsias (three out of our 12 patients experienced photopsias) that characterize CAR patients.

In Whitcup et al.’s study\(^{225}\), a patient with antibodies directed against recoverin produced strong labeling of the rods, cones, outer plexiform layer, and certain cone bipolar cells. Also, this patient had a strong cellular immune response against recoverin. Despite two years of extensive evaluation for malignancy, none was ever found. The authors suggested the term “recoverin-associated retinopathy” for their patient. Adding to this complexity, Peek et al.\(^{226}\) found antibodies that were reactive with Muller cells in a patient with progressive loss of vision over four years without malignancy. ERGs of both eyes showed greatly reduced b-waves. Keltner et al.\(^{161}\) described eight patients (only one with malignancy) who
displayed immunologic reactivity to a 22–kD antigen. A follow-up on case one of the studies is also presented in this report.

There are other reports of recoverin antibodies and other proteins found in retinal degeneration. Anti-recoverin immunoreactivity was found in 10 patients without malignancy from a sample pool of 521 patients with retinitis pigmentosa (RP). The authors conclude that there may be rare cases of CAR–like syndrome in the category of simplex RP and that these patients may also have anti-recoverin antibodies that could exacerbate their visual loss. However, Adamus points out in an editorial that these 10 patients had antibodies to multiple retinal proteins and that antibody titers were not measured to demonstrate the higher intensity or quantity of one antibody over others. The patients’ sera contained diffuse antibodies to retinal proteins; thus, it is difficult to assign a more important role to one protein than the others, but recoverin is a recognized potent autoantigen.

Although the presence of systemic autoimmune disease is not an inclusion criterion for ARRION syndrome, many of our patients have one or more systemic autoimmune disease. Those include patients with Jupus, a rare, but well documented, cause of optic neuropathy, celiac sprue, idiopathic thrombocytopenic purpura, rheumatoid arthritis, Sjogren’s syndrome, psoriasis, psoriatic arthritis and hypothyroidism. There has been reported a case of autoimmune retinopathy after chronic renal allograft rejection.

There is increasing evidence of autoimmune in other retinal disorders such as the white spot syndromes (WSS) (i.e. multifocal choroiditis/punctuate inner choroidopathy (MFC/PIC), acute zonal occult outer retinopathy (AZOOR), bird shot chorioretinopathy, multiple evanescent white dot syndrome, serpiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPE), acute macular neuroretinopathy, and relentless placoid chorioretinitis). Pearlman et al reported that there was an increased prevalence of systemic autoimmunity in both patients with WSS and their first and second-degree relatives. The authors suggest that WSS occur in families with inherited immune dysregulation that predisposes to autoimmunity.

ARRION patients may have a lifetime of dealing with numerous, recurring health–related issues. We previously reported a 22–kD patient, who was free of antibodies for 11 years while under immunosuppressive therapy. Although she recently developed recurrence of her immunologic ocular hypersensitivity to a new 45–kD reaction on Western blot and to outer segment photoreceptors on IFA, she does not appear to have cancer or further progressive visual loss. She remains under close surveillance for any visual changes.

Recently Ferreya reported a retrospective study of 30 patients with AIR with 11 of these nonparaneoplastic patients having cystoid macular edema (np/AIR/CME). The CME they reported showed on OCT demonstrated intraretinal cystic spaces or schisislike spaces, many of these case do not have leakage on fluorescein angiography, and they believe that patients with AIR macular changes re a forma of degenerative schisis. Heckenlively has reported in prospective masked studies that 90% of patients with RP and cysts have circulating antiretinal antibodies by means of Western blot analysis compared with 13% of patients with RP without macular cysts and 6% of controls. They also reported the personal autoimmune history of this cohort and the prevalence of autoimmune disease was 40% (12 of 30 patients). The breakdown of the personal autoimmune history was 6 of 13 (46%) in the nonparaneoplastic AIR (npAIR) group, 4 of 11 (36%) in the npAIR/CME, and 2 of 6 (33%) in the CAR group. We have reported similar phenomena in our ARRION patients. However, Ferreya did not report on the incidence of optic nerve antibodies in the patients. We like to use the term ARRION with CME for those AIR Patients who had CME and ARRION for those AIR patients without CME. The reason is stated above is that it is unclear if the antibodies generated from the retina and optic nerve are part of the etiology of the visual loss, or whether they truly represent an epiphenomenon to non–specific breakdown of retinal and optic nerve proteins. In this paper Ferreya reports that 21 out 30(70%) showed improvement with treatment. The treatment used was triple therapy using cyclosporine, azathioprine and prednisone which was given to those with a severe presentation. The typical doses used were 100mg/day for cyclosporine, 20to 40mgs/day for prednisone and 100mg/day for azathioprine. For patients with high clinical suspicion, but without classic presentation or positive Western blot information, the patients were treated with 1 or 2 subtenon periocular injections of methylprednisolone acetate 40 to 60 mgs in 1 eye as a clinical trial and then if there was clear improvement in that eye and antibodies were found to retina on Western blot, immunosuppressive therapy as outlined above was started. However, Jampol in an editorial following this article questioned whether the data reported by Ferreya really demonstrated this degree of visual improvement in these autoimmune visual loss patients.

The treatment for patients with ARRION syndrome is directed toward basic immunologic abnormalities, which consists of prednisone and other immunosuppressive therapies. The use of prednisone or IVMP may be considered the first treatment option. If this is not effective, the next standard immunotherapeutic approach is to follow the guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders, as outlined by the expert panel by Jabs et al. In addition, when necessary, IVlg and PE have been helpful in some patients. The use of IVlg in other immunologic diseases, CAR and MAR has previously been well outlined. Kurtz has reported on treatment of steroid dependent optic neuropathy with IVIG. The most
important aspect of treating patients with AARRRON syndrome is to be certain that they have progressive visual loss and no evidence of cancer. We have seen several patients with antibody reactions to the retina or optic nerve, but who appear to have visual loss that is stable; thus, the inciting factor appears to have been removed or is no longer a problem. Since these immunologic treatments are not benign and are also rather costly, it is essential to be sure that there is objective evidence of visual function loss before proceeding with treatment. The patient should also understand that there may not be a return of visual function, and that the goal of treatment may only be the prevention of further visual loss.

We have recently reported on a case of AARRRON syndrome treated with autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in a 47 year old woman with progressive visual and bearing loss. Clinical manifestations appeared to stabilize and may suggest that autologous HSCT may have a role in the treatment of AARRRON syndrome. In summary, autoimmune–related retinopathy and optic neuropathy (AARRRON) syndrome is probably much more common than has been previously recognized. Patients who are suspected of having autoimmune–related retinopathy and optic neuropathy should be evaluated first for the presence of cancer and given an ERG. If no cancer is found and appropriate immunologic testing demonstrates that the patient has antibodies to the retina or optic nerve, they may have AARRRON syndrome. Appropriate treatment may be necessary if patients show evidence of progressive visual loss. However, since all patients may not respond to steroid use, other immunomodulators may be necessary to slow or halt the deterioration of vision.

CME ANSWERS
1. E
2. C
3. E

REFERENCES


PARANEOPLASTIC DISORDERS CAUSING EYE MOVEMENT ABNORMALITIES

Shelley Ann Cross, MD
Mayo Clinic
Rochester, MN

LEARNING OBJECTIVES
1. To be able to recognize paraneoplastic ocular motility disorders.
2. To know the workup of these patients and the difficulties with diagnosis.
3. To have an idea about categories of treatment for these conditions.

CME QUESTIONS
1. What are the categories of paraneoplastic neurological disorders that are associated with eye movement abnormalities, and which motility disorders may be found?
2. How should a patient be evaluated for paraneoplastic disease?
3. What tests should be ordered on the CSF?

KEY WORDS
1. Paraneoplastic
2. Eye movements
3. Occult cancer

Paraneoplastic neurologic syndromes constitute a heterogeneous group of disorders which are manifestations of an immune response to a tumor. The pathogenesis is incompletely understood, but the body mounts an immune response directed against antigens which are shared between the tumor and normal tissue from the nervous system. Most of the identified antibodies are simply markers for paraneoplastic processes. They are not pathogenic. Including paraneoplastic and non-paraneoplastic autoimmune disease, there are only five disorders where the antibodies are truly causative and these are all disorders of peripheral nerve or the neuromuscular junction. They are:

1. PQ type voltage gated calcium channel antibodies in the Lambert–Eaton Syndrome (LEMS).
2. Acetylcholine receptor antibodies in myasthenia gravis.
3. Voltage gated potassium channel antibodies in neuromyotonia.
4. Ganglionic acetylcholine receptor antibodies in autonomic neuropathy.
5. Recoverin antibody found in carcinoma associated retinopathy.

The first four are not exclusively paraneoplastic as they can be seen without malignancy.
In some cases the presence of paraneoplastic antibodies seems to be associated with a better immune response against the tumor and actually a better overall clinical prognosis.
Paraneoplastic syndromes were at one time considered to be uncommon. With better understanding of what these disorders are, however, the frequency with which they occur is recognized to be more than previously thought. The more common syndromes such as Lambert Eaton Syndrome occur in as many as 3% of patients with small cell lung cancer. Myasthenia affects 15% of all patients with thymoma. For other solid tumors, the incidence is less than 1%. In the peripheral nervous system paraneoplastic disorders affect 5 to 15% of patients with plasma cell dyscrasias.

The paraneoplastic syndromes which cause abnormal eye movements are mostly those that affect the central nervous system with either an encephalomyelitis, cerebellar degeneration, or the syndrome of opsoclonus, myoclonus and ataxia. Other major categories of paraneoplastic disorders include the syndromes which affect the spinal cord and dorsal root ganglia including Stiff–Person Syndrome (with eye movement abnormalities), and the syndromes affecting peripheral nerve and muscle. In the latter, there may be oculomotor weakness, as in paraneoplastic Guillain Barre Syndrome, and, when there is autonomic pathology, pupillary and lacrimal problems may be seen.

Encephalomyelitis consists of involvement of multiple areas of the nervous system, most particularly including the temporal lobes and limbic areas, brain stem, cerebellum, spinal cord, dorsal root ganglia and autonomic nervous system. The distribution of lesions is patchy and varies greatly between patients. The pathology in general is a perivascular and interstitial inflammatory infiltrate of T–cells with gliosis, neuronophagic nodules and neuronal loss. A large majority of patients with encephalomyelitis have anti–Hu (antineuronal or ANNA–1). The most common associated cancer is small cell lung cancer which accounts for 75% of cancers associated with these clinical syndromes. Anti–Hu is particularly associated with myelitis and limbic encephalitis.
Ma2 associated encephalitis is particularly associated with testicular cancer. Patients have limbic, diencephalic and brain stem findings and daytime sleepiness is very common. Eye movement abnormalities, especially vertical gaze palsies, are frequently present and the patient's eye
movement abnormalities can progress to total external ophthalmoplegia. These eye findings should always prompt consideration of a paraneoplastic disorder, particularly if the findings are not classical for progressive supranuclear palsy. In 34 patients with these findings, 18 were found to have testicular germ cell tumors. In six men with Ma2 antibodies and negative detailed evaluation for malignancy, orchiectomy revealed microscopic testicular cancer. Some patients have midbrain involvement with a Parkinsonian syndrome with severe hypokinesis. Eye findings have not specifically been reported, but one would expect fixation disrupted by square-wave jerks, hypometria of horizontal and vertical saccades, normal saccadic velocity (except in advanced disease), impaired smooth pursuit, normal vestibular eye movements, impaired convergence, oculogyric crises, lid lag and reduced blink rate. Some patients in this group have coexisting antibodies to Ma1 and some of these patients with combined Ma1 and Ma2 antibodies have small cell lung cancer. Ma2 associated encephalitis has a better response to treatment than some other forms of paraneoplastic encephalitis, thus early diagnosis and recognition of the syndrome is important. 

Another form of limbic encephalitis is that associated with the NMDA receptor antibodies, particularly seen in patients with ovarian teratoma. These patients present with a subacute psychiatric syndrome with amnesia, seizures, dyskinesias, autonomic instability, loss of consciousness and hypoventilation.

Another form of encephalitis is seen in patients with voltage gated potassium channel antibodies (VGKC). These patients have autonomic dysfunction and neuromyotonia, REM sleep behavior abnormalities, and hyponatremia. This entity is an associated with thymoma and lung cancer.

CRMP-5 antibody is another antibody known to be a marker of encephalitis, peripheral mono-neuritis, dysautonomia, ataxia, myelopathy, optic neuritis and retinitis. It is most commonly associated with small cell lung cancer. In the 16 previously published case reports included in the article by Cross et al, 3 contained reports of nystagmus.

There are also patients reported in the literature with what clinically would be paraneoplastic encephalitis with serum antibodies which have not yet been identified. It is highly likely that there are many as yet unidentified antibodies which may be associated with patchy CNS inflammation. Any of these might be associated with inflammation in the brainstem, cerebellum and/or frontal and parietal lobes, and abnormal eye movements could be found. It is important to have a very high index of suspicion for a paraneoplastic disorder when seeing a patient with a new onset eye movement disorder.

Involvement of the brain stem can be seen in any of the above listed syndromes. Because this area may be affected with patchy inflammation, a wide variety of eye movement abnormalities can be seen including supranuclear palsy, intranuclear palsy, nuclear palsies, opcosolus, and nystagmus of various kinds. These eye findings may be accompanied by other cranial nerve abnormalities and other brain stem abnormalities.

Cerebellar degenerations constitute a second major group of paraneoplastic disorders affecting eye movements. These generally present rather acutely with dizziness, nausea, vomiting, gait instability, oscillopsia, diplopia and then gait and appendicular ataxia, dysarthria and dysphagia. Early in the clinical course, the MRI of the head is usually normal, although sometimes the folia enhance. Cerebellar atrophy follows. The CSF shows inflammatory changes. The cerebellar syndrome may coexist with a more widespread encephalomyelitis. Small cell lung cancer is the most common associated malignancy and is present in 80%. Some patients also have a Lambert–Eaton syndrome with peak Q voltage gated calcium channel antibodies. It is not clear why the cerebellum is such a frequent target of paraneoplastic auto-immunity, but certainly the outcome is devastating for the patient. Downbeat nystagmus is the most common ocular motility finding. Waveforms often have increasing velocity, suggesting an unstable neural integrator. Other findings include horizontal gaze–evoked nystagmus, impaired smooth pursuit, saccadic intrusions and dysmetria.

There are nine marker antibodies which have been associated with cerebellar syndrome. These include:

1. Anti-Yo (also called Purkinje cell auto-antibody type 1 or PCA1) associated with breast cancer, tumors of the ovary, endometrium, fallopian tubes, where the target of the antigens are CDR proteins expressed by Purkinje and tumor cells.
2. Anti–TR directed against a cytoplasmic antigen of Purkinje cells and associated with Hodgkin’s lymphoma and these may be detectible in CSF and not in serum.
3. Anti–Hu (ANNA–1) sometimes with associated anti–PQ antibodies and this is associated with small cell lung cancer and very severe disability. These two antibodies can be present in patients with and without LEMS. In the patients with LEMS, treatment seems to improve the LEMS but not the cerebellar degeneration.
4. Anti–CV2 (also called CRMP–5) which is directed against a cytoplasmic antigen and glial cells and is associated with a wide variety of central and peripheral nervous system symptoms and signs, including severe cerebellar degeneration and optic neuritis. These patients may also have, for example, peripheral neuropathy and encephalomyelitis.
5. Anti–MA–1 directed against a protein in brain and testes and associated with testicular as well as breast, colon and parotid tumors.
6. Anti-ZIC-4 also is commonly associated with CRMP-5 antibodies and associated with small cell lung cancer.
7. Anti-mGluR1 found in two patients with Hodgkin’s lymphoma.
8. Anti-CARP VIII (carbonic anhydrase related protein) associated with melanoma.

It is clear that the range of antibodies that can be associated with degeneration of the cerebellum and cerebellar eye findings is very large. In these paraneoplastic entities, the 14–3–3 protein is sometimes found in CSF, but this appears to be a bystander and is secondary to brain degeneration, not to Jakob–Creutzfeldt disease. This can cause clinical difficulties because paraneoplastic encephalitis and Jakob–Creutzfeldt disease may look similar clinically.

Treatment in these cases is very difficult and the results depend on which antibodies are present. Prognosis is worse for anti-Yo and anti-Hu and slightly better for anti-TR and anti-CV2. IVIG, cyclophosphamide and methylprednisolone, and Rituximab have been used.

A third major category of paraneoplastic disorders causing eye movement abnormalities is opsonoclonus myoclonus ataxia syndrome. This can be paraneoplastic, although it can also be due to effects from a virus, post–strept infection, metabolic abnormalities, metastases or intracranial hemorrhage. There are two main syndromes, a pediatric and an adult syndrome.

About 50% of children with opsonoclonus myoclonus have neuroblastoma, while 2% of children with neuroblastoma develop opsonoclonus myoclonus. Opsonoclonus myoclonus precedes the diagnosis of neuroblastoma in half. Patients who have this paraneoplastic syndrome have a better overall prognosis than those neuroblastoma patients who do not. Auto–immunity is believed to underlie the syndrome, but the antigens have not been identified. It appears that there are multiple antibodies directed against a variety of CNS antigens. Reported therapies include steroids, ACTH, plasma exchange, IVIG, and chemotherapy. Sixty% of children have residual behavioral abnormalities.

The adult syndrome is associated with truncal ataxia and brain stem and cerebellar signs. The MRI is usually normal, but there can be T2 signal in the dorsal, pons and midbrain. Cancers associated with this syndrome include small cell lung cancer, breast cancer (especially if also ANNA–2 positive), gynecological malignancies, lung and bladder cancer.

The pathophysiology of these eye movements remains unclear. Leigh and Zee discuss the traditional attribution of the movements to abnormalities in the cerebellum, specifically the fastigial nucleus. A newer idea that this disorder is caused by malfunction of pontine and midbrain pause cells. Glycine is the neurotransmitter of the omnipause neurons, and patients poisoned with strychnine, a glycine antagonist, show opsonoclonus and flutter. It is also possible that positive feedback loops and post–inhibitory rebound properties of premotor burst neurons are important in the generation of these eye movements.

Treatment has been attempted with clonazepam, thiamine and immunosuppressive drugs, as well as with immunosuppression with a protein A column. Anti–tumor treatment is also used. The prognosis is better with very prompt diagnosis and treatment. Unfortunately, the cerebellum can degenerate very quickly at which point the severe debilitating cerebellar findings are irreversible.

A fourth major category is that of the visual syndromes, including CAR, MAR and paraneoplastic optic neuropathy. These are being discussed by Dr. Keltner.

There is a group of syndromes affecting the spinal cord and dorsal root ganglia. These include motor neuron syndromes of subacute motor neuronopathy and ALS type syndromes which are atypical because the CSF protein is elevated. There is a lymphoproliferative picture in blood and there may be M–protein spike. These findings raise the suspicion that what presents as ALS might in fact be paraneoplastic. Other spinal cord and dorsal root syndromes include Stiff Person Syndrome and subacute sensory neuronopathy.

Amongst this group of paraneoplastic disorders, Stiff-Person Syndrome should be considered in patients with new eye movement abnormalities. The classical form of this disorder is characterized by progressive muscle stiffness, rigidity and spasm, particularly involving axial muscles. The spasms are triggered by various stimuli. EMG shows continuous discharges of motor unit potentials. In addition to the classic motor abnormalities, these patients can have involvement of the brain with a cerebellar syndrome, an extrapyramidal syndrome, and an encephalitic picture. Diagnosis of a functional disorder is, unfortunately, quite frequent. There are three recognized subsets of this disorder:

1. An autoimmune variant associated with GAD–65 antibody, type 1 diabetes mellitus and other autoimmune disorders.
2. A paraneoplastic variant associated with the amphiphysin antibody, seen particularly in patients with breast and small cell lung cancer.
3. An idiopathic variant without an identifiable antibody (35% of cases).

Eye movement abnormalities are quite varied. This depends on the specific parts of the nervous system affected. A confounding factor is whether there are eye movement abnormalities associated with any of the autoimmune disorders which may coexist with Stiff Person Syndrome (such as myasthenia gravis and thyroiditis).

Nystagmus (including downbeat nystagmus with
concomitant ataxia), alternating skew deviation, (in the presence of ataxia), dysmetric saccades, oscillopsia, poor smooth pursuit, slow following movements, limited up and down gaze, and vertical and horizontal misalignment have all been reported. Oskarsson et al have reported a case of non-paraneoplastic Stiff–Person Syndrome with extrapyramidal features and anti GAD–65 antibodies in which they have recorded eye movements. The patient had a supranuclear vertical gaze palsy, vertical greater than horizontal hypometric saccades with prolonged saccade latency, saccadic vertical pursuit but normal horizontal pursuit and impaired convergence.

A further group of syndromes are those affecting **peripheral nerve and muscle**. In the peripheral nervous system, we can find subacute sensory neuropathy, chronic sensorimotor neuropathy associated with plasma cell dyscrasias, acute sensory motor neuropathy (Guillain–Barre), paraneoplastic autonomic neuropathy and paraneoplastic peripheral nerve vasculitis. A vasculitic syndrome can certainly involve cranial nerves III, IV and VI and can cause cranial nerve palsies.

**Muscle syndromes/myoneural junction syndromes** include myasthenia gravis with acetylcholine receptor antibodies associated with thymic hyperplasia and thymic epithelial tumors and also with small cell lung cancer, thyroid, breast cancer and Hodgkin lymphoma. There is also Lambert–Eaton myasthenic syndrome where antibodies are directed against voltage gated calcium channels. This presents with hip and then shoulder girdle weakness, muscle stiffness and myalgias, autonomic dysfunction, dry mouth and impotence. Oculobulbar symptoms can be present, but are relatively mild in contrast to true myasthenia gravis where they are sometimes much more severe. Fifty % of patients with Lambert–Eaton have cancer, usually small cell lung cancer. Treatment of the muscle symptoms includes guanidine and pyridostigmine, IVIG and immunosuppression. Other muscle syndromes include dermatomyositis and polymyositis, paraneoplastic neuromyotonia, acute necrotizing myopathy and cachetic myopathy.

It is, first of all, imperative to consider paraneoplastic disorders when seeing a patient with a new ocular motility disturbance. Since malignancy can present with paraneoplastic disease, no past history of tumor is required. Even disturbances which superficially fit a diagnosis of a degenerative disease or vascular disorder should have paraneoplasia considered. Although paraneoplastic processes are often characterized as “subacute”, i.e. in the category of inflammatory disease, sometimes symptomatically they are more “acute” (like vascular disease) or more “chronic” (like degenerative disease). When the picture is not classical for anything, this is the time to think of a paraneoplastic process.

The evaluation of patients with paraneoplastic syndrome is challenging. Routine blood work should be supplemented by an antibody panel. A standard panel of antibodies should be screened for, rather than a certain few. The reason for this is that a single syndrome can be associated with multiple different antibodies and a single antibody can be associated with more than one clinical syndrome.

Because antibodies may be absent in the serum but present in the CSF, the CSF should be subjected to the antibody panel screening as well. A lumbar puncture also allows for measurement of inflammatory markers, white cells, red cells, elevated protein, which can be very suggestive of a paraneoplastic process.

The MRI of the brain is sometimes useful. Early in the clinical course the MRI of the brain can be negative, but later there can be enhancement of involved areas, particularly in the encephalomyelitis and the cerebellar degeneration groups. In patients with opsoclonus, myoclonus, and glioblastoma, the tumor will be seen. In patients who have peripheral nervous system disease, nerve conduction and EMG are helpful. Nerve biopsy can be invaluable as well.

It is essential to do a very thorough search for a primary tumor, including CT scanning of the chest, abdomen and pelvis. In males, testicular ultrasound may be indicated. In women or men with or without palpable breast masses, mammography is essential. If these studies are negative, PET scanning may be of value. It can be sensitive in finding small areas of occult malignancy. Enlist the help of a colleague in internal medicine to help with detection of other immune processes and occult tumor.

The hunt for an occult primary can be extremely frustrating. In some cases, it is necessary to repeat this testing after a number of months have gone by. As mentioned above, in patients with testicular lesions, these can be so tiny as not to be findable in any way except for a pathological study of the testicles. Even more frustrating is the idea that in some patients these syndromes will exist and no primary tumor will ever be found.

Treatment is equally frustrating. There are two major ways of approaching treatment. The first is identification and treatment of the primary tumor. The second involves suppression of the immune response. In the group of peripheral nerve disorders, response to IVIG, plasmapheresis and immunosuppression is often reasonable. In disorders that are antibody mediated, namely the four or five disorders of neuromuscular junction and retina, B–cell treatment with Rituximab might be of benefit. For the other disorders, however, we are left with IVIG, plasmapheresis, immunosuppression, steroids and immunosuppression with drugs such as cyclophosphamide, tacrolimus and Cyclosporin. The earlier these disorders are discovered, the better the potential for prevention of worsening, however, many of them just are not treated satisfactorily in any way and particularly the cerebellum has degenerated, there is no going back.
**CME ANSWERS**

1. Encephalomyelitis, cerebellar degeneration, the syndrome of opsoclonus, myoclonus and ataxia, spinal cord and dorsal root ganglia (Stiff–Person Syndrome) and peripheral nerve and muscle (paraneoplastic Guillain Barre Syndrome)

2. Evaluations should include routine blood work and urinalysis, a full paraneoplastic antibody profile, CXR, CT of chest abdomen and pelvis, MRI of brain, lumbar puncture, PET scanning (if other tests are negative), testicular ultrasound (males) and mammogram (females, males with breast lesions).

3. Glucose, protein, cell count, flow cytometry and cytology, paraneoplastic antibody panel.

**REFERENCES**


LEARNING OBJECTIVES
After reviewing these materials, the attendee should recognize:

1. The three intervals from treatment (first month, second–sixth months, and greater than six months) and the infectious, vascular, and immune problems, particularly those affecting the eyes, that occur at these times.

2. The diversity of manifestations of common infections such as varicella zoster virus (VZV) and progressive multifocal leukoencephalopathy (PML) and their associated ophthalmic issues.

3. The spectrum of neurologic and neuro-ophthalmic complications of graft vs. host disease (GvHD), as well as the phenomenon of immune reconstitution inflammatory syndrome (IRIS).

CME QUESTIONS
1. Progressive multifocal leukoencephalopathy can be seen in the setting of:
   A. Long-term immune suppression by HIV
   B. Chronic corticosteroid use for lupus
   C. Long-term survival after HCT for leukemia
   D. Use of natalizumab for multiple sclerosis
   E. All of the above

2. The most common ocular manifestation of chronic graft versus host disease is:
   A. Retinal vasculitis
   B. Keratoconjunctivitis sicca
   C. Cataract
   D. Fungal endophthalmitis
   E. Cytomegalovirus retinitis

3. Possible neurologic complications of Aspergillus infection include:
   A. Ischemic optic neuropathy
   B. Subarachnoid hemorrhage
   C. Stroke
   D. Spinal cord infarction
   E. All of the above

KEY WORDS
1. Allogeneic transplantation
2. Autologous transplantation
3. Progressive multifocal leukoencephalopathy
4. Graft versus host disease
5. Immune reconstitution inflammatory syndrome (iris)

INTRODUCTION
Hematopoietic cell transplantation (HCT) has become the preferred treatment for an increasing number of neoplastic as well as non–malignant diseases. HCT refers to the intravenous infusion of progenitor cells to restore bone marrow function eradicated by chemotherapy given for the underlying disease. The progenitor cells can be obtained from a matched human leukocyte antigen (HLA) donor (allogeneic transplantation) or obtained from the patient prior to the chemotherapy (autologous transplantation). Worldwide 30,000 autologous transplantations are done annually, 2/3’s for non-Hodgkins lymphoma and multiple myeloma, while more than 15,000 allogeneic transplantations are performed, about 1/2 for acute leukemia.

Progenitor cells can be harvested from the bone marrow or from peripheral blood cells after administration of hematopoietic growth factors. Allogeneic transplant recipients require chronic immunosuppression to prevent rejection and graft vs. host disease (GvHD). Autologous transplant recipients do not require immunosuppression but to reduce the incidence of relapse due to contaminant tumor cells, CD34+ selection has been used and is associated with slower reconstitution of the immune system which may lead to a higher rate of infectious complications. Based on data demonstrating an anti–tumor effect of the graft–versus–tumor response, regimens with lower dose nonmyeloablative conditioning have been developed in the last 10 years. Such reduced–intensity stem cell transplantation (RIST) for older or more ill patients also likely will be used for increasing numbers of patients with nonmalignant conditions and is likely to be associated with less neurotoxicity. This discussion will focus on complications of most relevance to neuro–ophthalmologists classified on the basis of degree and type of immunosuppression and time since the transplantation. While this is a logical way to address a neurologic problem, other factors such as underlying disease, donor origin, and type of conditioning regimen will all affect the neurologic differential diagnosis and outcome.
Overview of Neurologic Complications
The frequency and variety of complications vary in different series depending on whether authors consider just hematologic disease, study allogeneic or autologous HCT, include autopsy findings and include children in the study population. For example, in one large series by Denier et al of 361 consecutive patients (245 autologous, 116 allogeneic) with either hematologic malignancies or solid cancers, sixteen percent developed symptomatic neurologic complications, more often in the allogeneic group. CNS infections were the most common problem and usually occurred in the first 4 months. Factors increasing the risk of developing a HCT–related neurologic complication include severe GvHD, the use of total body irradiation for conditioning or pretransplant chemotherapy including intrathecal methotrexate, a diagnosis of acute myelogenous leukemia (AML) and prolonged immunosuppression.

Complications During Stem Cell Harvesting: Medical Procedures and Drug Toxicity
Harvesting of stem cells from bone marrow or peripheral blood is very safe. A rare complication of bone marrow aspiration is unintended entry into the subarachnoid space. The phenomenon of intracranial hypotension results in positional headache and sometimes diplopia with a characteristic diffuse dural enhancement which should not be misinterpreted as infectious or neoplastic meningitis. Internal jugular cannulation can result in Horner’s syndrome and occasionally lower cranial nerve palsies.

Complications During Conditioning and Infusion of Stem Cells
High–dose chemotherapy and totally body irradiation during myeloablation are the cause of most neurologic complications during this period. Common conditioning regimens include drugs with neurotoxicity. Ifosfamide may cause visual and auditory hallucinations, encephalopathy and seizures that can begin during the infusion and are treated with methylene blue. Busulfan–treated patients (sickle cell disease and thalassemia) are routinely treated with antiepileptic drugs to prevent seizures. Patients receiving carmustine may develop ischemic optic neuropathy or retinal microvasculopathy.

Patients with an underlying autoimmune disease such as multiple sclerosis, systemic lupus erythematosus, or chronic inflammatory demyelinating polyneuropathy may have an exacerbation of their disease while receiving recombinant human granulocyte colony–stimulating factor. The concurrent use of cyclophosphamide may decrease the risk of disease exacerbation.

During the infusion of stem cells there are reports of reversible posterior leukoencephalopathy syndrome (RPLS, see below) and stroke. These events are postulated to be due to dimethylsulfoxide (DMSO) used in the cryopreservation.

THE FIRST MONTH: COMPLICATIONS DURING PANCYTOPENIA
This is the period of greatest risk for infection when 87% of CNS infections occur.

The clinician should consider the “net state of immunosuppression” by which we mean the sum of all the risk factors that patient bears. These include exogenous immunosuppression with corticosteroids and calcineurin inhibitors and/or mycophenolate, complications of surgery (nosocomial infections), underlying immune deficits, viral co–infections (cytomegalovirus (CMV) and hepatitis B/C), and pre–existing exposures in donor or recipient.

Donor–derived infections have been the cause of several transplant–associated deaths in the past two years. These have included West Nile Virus, Lymphocytic choriomeningitis virus, and rabies as well as human herpesvirus 6 encephalitis (see below). All these infections occurred within the first month after transplantation and are nicely reviewed in a two part article on emerging viral infections by Tyler.

Before engraftment and during prolonged cytopenias, patients may have subdural hematomas. Though they may not mount much of an inflammatory response and the CSF may be rather misleadingly bland, these patients are at risk for bacterial meningitis during this period, most commonly due to hospital–acquired Staphylococci or gram negative organisms. Other pathogens include Pneumocystis jiroveci and Listeria monocytogenes, though the widespread use of trimethoprim–sulfamethoxazole has reduced the risk of these infections

In the early posttransplant period the major event is the engraftment syndrome which must be distinguished from post transplant acute limbic encephalitis (PALE). Engraftment occurs 2–4 weeks post transplant when there is upregulation of cytokines by neutrophils after colony stimulating factors are employed. There is rash, fever, and headache as the absolute neutrophil count exceeds 500. This syndrome must be differentiated from that of acute limbic encephalitis whose major manifestations are transient amnesia, confusion, and/or seizures. While there are several cause, including paraneoplastic syndromes, herpes simplex virus and human herpesvirus 6 (HHV6), encephalitis, status epilepticus and Wernicke’s encephalopathy, the most important treatable etiology is HHV6.

Human herpesvirus 6 encephalitis is the putative cause of PALE and may present with visual hallucinations. Most disease represents a reactivation of host infections, though allograft transmission has been reported. Consequences of this infection include delayed platelet recovery, reactivation of hepatitis C and reactivation of cytomegalovirus (CMV). Mortality can be as high as 40% and the disease is more common when the conditioning regimen include antithymocyte globulin, sirolimus or inteleukin–12 antibodies and when there is severe GVHD in grafts from unrelated donors. The treatment is ganciclovir or foscarnet.
THE FIRST MONTH: SPECIAL NEURO-OPTHALMOLOGIC CONCERNS

The following four entities occurring during this early interval after transplantation (and sometimes later) are of special concern to neuro-ophthalmologists:

1) **Pseudotumor cerebri** (PC), also known as benign intracranial hypertension or idiopathic raised intracranial pressure, often dictates neuro-ophthalmologic consultation because of the headache, blurred vision and papilledema with which it presents. This is a diagnosis of exclusion, after neoplastic, viral, fungal, and bacterial etiologies are eliminated, but in the allogeneic bone marrow transplantation setting, cyclosporine can be associated with PC. Two children, both obese, who received match sibling donor grafts developed markedly raised pressure which resolved with cessation of cyclosporine and replacement with mycophenolate or tacrolimus along with steroids and/or acetazolamide.7 We have seen one adult with this problem in whom the raised intracranial pressure resolved after discontinuation of cyclosporine, the levels of which were in the appropriate therapeutic range at the time of the events.

2) **Immune reconstitution syndrome**

Immune reconstitution inflammatory syndrome (IRIS) was first described in the context of HIV-associated immunodeficiency in immune function with highly active anti-retro-viral therapy (HAART). Patients with various systemic and CNS infections experience recrudescence of symptoms often with more dramatic elevation in CSF pressure and pleocytosis in the context of cryptococcus, neurosyphilis, progressive multifocal leukoencephalopathy, and tuberculosis.8 IRIS may occur during either of two phase of immune restitution. The first period of susceptibility is in the initial weeks when the increase in CD4+ T cells occurs and the second which may last for as long as 2 years. An incidence of IRIS has been reported between 15 and 45% of patients receiving HAART (all neurologic and systemic symptoms mixed together).9

The phenomenon of IRIS is becoming relevant to the transplant and other aggressively treated hematologic and solid tumor populations. Alemtuzumab a humanized anti-CD52 monoclonal antibody that causes profound T and B lymphocyte depletion and neutropenia that may last (at least for CD4+ T cells) for more than one year, has led to case reports of IRIS with both systemic and neurologic involvement after initial cryptocoecal meningitis treatment.10

IRIS affecting the eye has been documented in association with CMV retinitis in a large number of HIV patients. This syndrome is referred to as immune recovery uveitis which is presumed to be mediated by recovery of immune response to specific residual CMV antigen in the eye. As in the case of systemic IRIS, a low CD4 T cell count at the time of HAART initiation is a risk factor.11 Immune recovery uveitis to CMV also has been reported in the transplant population and the risk can extend well beyond the transplant period and be confused with intraocular lymphoma (see below).12

3) **Marginal keratitis** can occur in the setting of engraftment syndrome. The presentation may be a combination of rapid white blood cell count recovery, fever, skin rash, shortness of breath and conjunctival injection with, in a case described by Dai et al, bilateral corneal subepithelial infiltrates particularly in areas of corneal pannus from previous contact lens related neovascularization.13 In the case described there was no uveitis, ocular bacterial and viral cultures were negative and a conjunctival biopsy was negative for ocular GVHD and viral inclusions. Treatment with topical corticosteroids showed complete resolution.

4) **Reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome (PRES)** has been discussed in the previous lecture and is appropriately re-emphasized here as it is closely associated with a number of the agents used in immunosuppression for HCT (cyclosporine, tacrolimus, sirolimus, bevacizumab, high–dose corticosteroids, etc). Ocular symptoms suggestive of cortical blindness figure prominently in the clinical symptom complex.

ONE TO SIX MONTHS POST TRANSPLANTATION

While the risk of bacterial infection declines during this period, fungal, parasitic, and viral disease incidence rises. Aspergillus becomes a prime concern, producing a spectrum of clinical manifestations including headache, sinusitis, mass lesions, septic embolism, and subarachnoid hemorrhage from infectious aneurysms. Headache and cranial neuropathies including visual deficits may bring the patient to the neuro-ophthalmologist. A recent New England Journal of Medicine CPC illustrates the diagnostic dilemma posed by Aspergillus in the case of a 68 year old transplant recipient with a painful, progressive prednisone-responsive monocular visual loss funduscopically resembling anterior ischemic optic neuropathy and initially thought to be giant cell arteritis. However, the patient developed evidence of sphenoid sinusitis followed in rapid succession by evidence of brainstem infarction then massive subarachnoid hemorrhage and aneurysm development in the vertebrobasilar system. At postmortem there was infarction of the right optic nerve.14

This case illustrates the dangers in assuming an active autoimmune disorder such as GCA in a patient immunosuppressed for transplantation or on dose–intensified corticosteroid therapy. The spectrum of potential pathogens is very broad. CSF cultures are almost always negative. Sino–orbital aspergillosis is a life-threatening condition with involvement of the intracranial space via the superior orbital fissure and optic canal. Treatment is usually a combination of surgical debridement and intravenous amphoricin B, though a case...
of responsiveness to oral itraconazole has been reported in a case similar to the one discussed above with visual loss initially preceded by headache and ascribed to giant cell arteritis.15 Several examples of Aspergillus behavior with visual loss will be presented in the slides.

Another organism that spreads from sinuses to brain and produces vascular invasion with infarction is mucor, a devastating infection caused by Mucor Rhizopus and Absidia. Thrombosis, infarction, and necrosis with spread to brain, and facial numbness are the hallmarks of presentation in the setting of diabetic ketoacidosis. The case of a 12 year old on azathioprine and prednisolone with diplopia, otalgia and right facial numbness followed by right eye blindness treated successfully with amphotericin B, oral posaconazole, and intrathecal amphotericin B will be shown.16

Finally Varicella Zoster virus (VZV) and its many neurologic manifestations can be a significant risk in the period immediately after engraftment and reconstitution. However, the risk of VZV continues well into the period after the first six months. Dermatomal or disseminated skin lesions are the most common manifestation followed by Ramsay–Hunt, segmental pontine myelitis, acute necrotizing encephalitis, and acute retinal necrosis.17 Numerous vascular events including a combination of large and small vessel cerebral strokes should suggest VZV as an etiology. Viral transport retrograde from trigeminal ganglia to middle cerebral artery is the mechanism of infection. CSF reveals lymphocytic pleocytosis with positive IgG antibody and arteriography shows focal narrowing and beading of vessels. CSF pleocytosis is absent in one third of cases. Rash is not required for diagnosis. Spinal stroke can be ascribed to VZV, an example will be shown in the slides. Confirmation of VZV vasculopathy requires DNA by PCR or more commonly of anti-VZV in the IGG in the CSF.18

Several VZV syndromes are of particular interest to neuro–ophthalmologists:

1) Acute retinal necrosis can be caused by VZV, HSV1 or HSV 2. Patients present with periorbital pain and floaters with loss of peripheral vision due to an occlusive vasculopathy with prominent inflammation in the anterior chamber. Progressive outer retinal necrosis from necrosis from VZV is the second most common opportunistic retinal infection among Northamong American AIDS patients (CMV is the most common). Rapid painless visual loss, the relative absence of intraocular inflammation, floaters and constricted fields due to retinal detachment are seen. Involvement of the fellow eye can follow within weeks. There is no occlusive vasculitis in this entity. Diffuse retinal hemorrhages and whitening with macular involvement are characteristic (slide will be shown). Patients are treated with combined intravenous ganciclovir and foscarnet and will worsen with corticosteroid treatment.

2) Acute monocular visual loss with occlusion of the central retinal artery 2–4 weeks after trigeminal distribution zoster.

3) VZV associated cranial nerve disease: like large vessel stroke, the vasculopathy of arteries supplying one or more cranial nerves occurs weeks after the acute zoster infection due to vascular infection of infection of branches of internal carotid supplying III, IV, V and VI.

MORE THAN SIX MONTHS POST TRANSPLANTATION

Many ocular complications may occur at this interval out from transplantation and contribute significantly to quality of life after transplantation. Best–corrected visual acuity at 1 year after HCT was less than 20/200 in 16% of patients in one study and less than 20/50 in 21% of the 620 patients in that study.19 The table below summarizes the ocular complications in that report:

TABLE 2: Ocular Complications in 620 Patients Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation*

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>GVHD</th>
<th>Dry eye syndrome (without GVHD)</th>
<th>Corneal ulcers</th>
<th>Steroid-induced cataract/ glaucoma</th>
<th>Cytomegalovirus retinitis</th>
<th>Acquisation of allergic conjunctivitis</th>
<th>Uveitis</th>
<th>Fungal endophthalmitis</th>
<th>BMT</th>
<th>CMV</th>
<th>EBV</th>
<th>HSV</th>
<th>CMV</th>
<th>VZV</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>34 (5.5)</td>
<td>30 (4.8)</td>
<td>15 (2.4)</td>
<td>14 (2.3)</td>
<td>4 (0.7)</td>
<td>4 (0.7)</td>
<td>7 (0.9)</td>
<td>1 (0.2)</td>
<td>21 (3.4)</td>
<td>9 (1.5)</td>
<td>10 (1.6)</td>
<td>2 (0.3)</td>
<td>5 (0.8)</td>
<td>6 (0.9)</td>
<td>8 (1.3)</td>
</tr>
</tbody>
</table>

Tabbara et al, Reference 19.

In a pediatric study from Sweden, cataract risk was reported to be increased after conditioning with total body radiation compared to chemotherapy with busulfan and there was an increased risk of cataracts if treated with single dose total body irradiation (TBI). Fifty eight percent of the patients treated with TBI develop different grades of cataract and the majority who received single dose TBI required surgery. In this study there was no relationship between total dose and duration of steroid therapy and cataract development. Regular ocular examinations are necessary to detect and treat complications and avoid amblyopia.20
SPECIAL NEURO-OPHTHALMOLOGIC CONCERNS

> 6 MONTHS POST HCT

1) **Graft vs. host disease (GvHD)** is one of the major hazards after HCT. It involves many organs, most frequently skin liver GI tract and eyes. Ocular GVHD can be classified as acute (during the first 3 months) or chronic, the latter being much more common. Up to 60–80% of chronic graft versus host disease patients will have an ocular complication which can encompass any part of the eye from the lid to the choroid. Ocular GVHD is most commonly considered a disease of the ocular surface. The most common ocular manifestation is keratoconjunctivitis sicca which may be the presenting symptom. Lacrimal gland insufficiency is common. Retinal microvascular occlusive disease is less commonly seen.21

2) **Anterior uveitis** has been described after conventional and also nonmyeloablative allogeneic HCT. This usually occurs during an exacerbation of chronic GVHD. Elevated levels of inflammatory cytokines IL–6 and IL–10 have been found in patients’ocular fluid at times of uveitis. It is unlikely that these abnormalities were due to medications.22 Treatment of ocular GvHD is both systemic and topical. With the increasing use of nonmyeloablative allogeneic HCT ophthalmologists may encounter a different distribution of ocular complications from that found in more conventional bone marrow transplantation. Instead of cataract and radiation retinopathy, chronic ocular surface disease and anterior uveitis may be the more frequent complications and must be recognized promptly to prevent irreversible eye damage.

3) **CMV retinitis** is the most common infectious ocular complication of HCT. CMV retinitis presents as retinal whitening with hemorrhage and vasculitis. The differential diagnosis includes lymphoma, herpes simplex and VZV as well as other infections such as toxoplasmosis and syphilis. Gooi and colleagues report a case of CMV retinitis mimicking lymphoma that was definitively diagnosed by a retinal biopsy whose limited amount of tissue was destained to perform additional immunohistochemical studies.12 Alternatively, PCR studies on an aqueous humor sample or vitreous aspirate could show CMV.23

4) **Progressive Multifocal Leukoencephalopathy (PML):** It is appropriate to end this discussion with what is emerging as one of the most variable and difficult to diagnose and treat conditions facing the transplant population. First described in 1957, PML is due to a papova virus (JC virus after the initials of a patient from whom the virus was isolated in 1971). It has been suggested that since the disease is not always progressive, often not multifocal, and may involve gray matter as well, that the name be changed to JC virus encephalopathy.24 With the advent of HIV epidemic, PML was recognized as a major opportunistic infection that now threatens diverse groups of patients, including those on natalizumab for multiple sclerosis or Crohn’s disease.

Equally importantly, PML has been seen in HIV negative patients after rituximab therapy (a monoclonal anti B cell antibody used in lymphoma and other hematologic malignancy treatment as well as in multiple sclerosis). To date, at least 57 patients with lymphoproliferative disorders and several with rheumatoid arthritis and lupus have developed PML after treatment with rituximab in addition to the 14 multiple sclerosis cases reported.25 The diversity of radiographic manifestations of PML reflects the variability of underlying immune deficit in the affected patients and ranges from white matter lesions without enhancement or mass effect to tumor–like lesions with vivid gadolinium uptake. A common presentation is slowly progressive focal deficit often with visual features or, less commonly, a progressive brain stem syndrome. The phenomenon of immune reconstitution in PML–affected patients raises further issues and the role of steroids to suppress inflammation, pioneered in HIV patients, remains a point of debate.26

Several examples of diverse presentations of PML in different clinical settings will be shown, including 1) a patient who developed PML after only 3 cycles of CHOP–Rixtubimab chemotherapy for lymphoma; 2) a patient on minimal immunosuppression 2 years after HCT for AML; 3) a patient whose only immune defect appeared to be a low CD8+ count; and 4) a patient with HIV who presented with an hemianopia and neglect with a large contrast enhancing mass lesion mimicking glioblastoma that was due to PML–IRIS.

While there is no established treatment for PML, reduction in immunosuppression may result in clinical and radiologic improvement. Isolated reports of continuous infusion interleukin–2 have been encouraging. More recently, the recognition that the 5–hydroxytryptamine 2a serotonin receptor is a cellular receptor for JC virus has led to trials of the serotonin receptor antagonist mirtazapine.

**CONCLUSION**

Though hematopoietic cell transplant procedures have made major progress in the control of many previously fatal illnesses, multiple neurologic complications both long known and recently recognized continue to threaten the quality of life of survivors. Both neurologists and neuro–ophthalmologists play a major role in evolving management of these complex conditions.

**CME ANSWERS**

1. E
2. B
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REFERENCES


LEARNING OBJECTIVES
1. Be able to identify the clinical syndromes reported with toxicity from chemotherapeutic agents.
2. Understand the characteristic side effects of the chemotherapeutic agents most commonly reported to cause neurotoxicity.
3. Identify potential strategies to limit neurotoxicity from chemotherapeutic agents.

CME QUESTIONS
1. Which of the following statements is most consistent with neurotoxicity from a chemotherapeutic agent?
   a. Encephalopathy is readily distinguished from other causes not related to chemotherapy
   b. Neurotoxicity from a suspected chemotherapeutic agent is often easily identifiable
   c. Toxic optic neuropathy is the mechanism uniformly described to cause visual loss
   d. Neurotoxicity from chemotherapeutic agents may be acute or delayed
2. Intrathecal administration of methotrexate has been most commonly reported to cause neurotoxicity from:
   a. Aseptic meningitis
   b. Toxic optic neuropathy
   c. Ophthalmoplegia
   d. Nystagmus
3. Which of the following statements best characterizes interventions to limit neurotoxicity from chemotherapeutic agents?
   a. Advancing an arterial infusion catheter beyond the ophthalmic artery may increase the risk of ischemic ocular side effects of chemotherapy
   b. The risk of neurotoxicity is lower when methotrexate is given prior to rather than after radiation therapy
   c. Amifostine has been proven to limit chemotherapy–induced peripheral neuropathy
   d. Neuroprotective agents have been shown to be definitively effective in clinical trials

KEY WORDS
1. Chemotherapy
2. Toxicity
3. Optic neuropathy
4. Leukoencephalopathy

INTRODUCTION
Patients with cancer not infrequently develop neurologic or ophthalmologic conditions. With the use of more aggressive treatment regimens and prolonged survival of patients with cancer, neurotoxicity related to chemotherapy has been thought to be increasing in frequency.1 These patients often have received multiple different treatments, including chemotherapy, radiation therapy (RT), and bone marrow transplantation (BMT). Therefore, establishing the etiology of the neuro–ophthalmic problem may be quite complex. One possibility is a direct effect of the cancer itself, either by metastasis or local effects. A remote paraneoplastic syndrome is another. Direct toxicity may occur from chemotherapy or RT. Toxicity may be a secondary effect, such as a drug–induced hemorrhage from thrombocytopenia or an infection from immunosuppression. Metabolic disturbances from multiple causes can produce systemic, neurologic, and ocular deficits, and multiple treatment modalities may be additive in causing neurologic or ophthalmologic toxicity. A complete history of all of the medications a patient is using may be important as some unconventional therapies may also have neurotoxicity. Finally, the possibility always exists that the new symptoms are totally unrelated to the cancer or its therapy.2

GENERAL CONSIDERATIONS
Chemotherapeutic agents typically act on rapidly dividing tumor cells. Because the majority of cells in the brain and spinal cord, including neurons and astrocytes, undergo little cellular division, acute effects of many chemotherapeutic agents are less prominent in the central nervous system (CNS) than in other organs.1 Another factor protecting the CNS from toxicity is the blood brain barrier (BBB), which limits the amount of ionized and water soluble drug that can reach the brain.3 Nonetheless, neurologic toxicity is frequently observed and is often the dose limiting side effect of the treatment.4
In addition to the inherent toxicity of a chemotherapeutic agent, the mechanism of delivery of the drug is important in determining its toxicity. Intrathecal, intracameral, and intra arterial delivery are more likely to be associated with toxicity than are oral or intravenous routes.

New innovations provide for enhanced delivery of chemotherapy, but these can also increase the potential toxicity of the drug being given. Continued development of neuroprotective agents may also enable the use higher doses of chemotherapeutic agents.

The emergence of sophisticated supportive care techniques, including blood banking and transfusion, the use of protected environments, improved antibiotics and immunosuppressive agents, and a greater understanding of drug pharmacokinetics have allowed the development of new strategies for the treatment of cancer. For example, significantly higher chemotherapy dose regimens, previously fatal by virtue of myelosuppression, are possible because of the potential for BMT.

The following sections highlight the toxicities of a variety of chemotherapeutic agents, separating them by their normal biologic activity against cancer cells. These drugs include antimetabolites, alkylating agents, antibiotics, and plant alkaloids. I have focused on the agents that have been more commonly reported to cause neurotoxicity and have largely omitted corticosteroids, biologic agents, growth factors, small molecules and monoclonal antibodies.

DIFFICULTIES WITH EXISTING LITERATURE

I have constructed a table (Table 1) of the neuro-ophthalmic side effects of chemotherapeutic agents, in part adapted from two prior references. A thorough review of the ocular complications of chemotherapy was published in 2006, and also contains a list of the common combinations of drug therapy and a table of the malignancies and their typical drug treatments. There are excellent reference texts on chemotherapy agents and more specifically, their neurologic side effects.

### TABLE 1: Neuro-ophthalmic side effects of chemotherapeutic agents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>More Common Side Effect</th>
<th>Less Common Side Effect</th>
<th>Reported Ocular Toxicity</th>
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<td>5-Fluorouracil</td>
<td>Pyrimidine antimetabolite</td>
<td>Acute cerebellar syndrome</td>
<td>Myelopathy with intrathecal therapy</td>
<td>Periocular edema</td>
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<td>Eye pain</td>
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<td>Lacrimal duct stenosis / epiphora</td>
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<td>Blepharospasm</td>
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<td>Ocular motor disturbance</td>
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<td>Nystagmus</td>
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<td>Blurred vision</td>
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<td>Decreased visual acuity</td>
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<td>Diplopia</td>
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<td>Photophobia</td>
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<td>Anastrozole</td>
<td>Nonsteroidal aromatase inhibitor</td>
<td>Headache</td>
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<td>Retinopathy</td>
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<td>Bevacizumab</td>
<td>Monoclonal antibody to vascular endothelial growth factor</td>
<td>Headache</td>
<td>Thromboembolism Posterior reversible leukoencephalopathy</td>
<td>Visual hallucinations Retinal pigment epithelial tears and other complications of intravitreal injection</td>
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<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Painful senory neuropathy</td>
<td>Rarely posterior reversible leukoencephalopathy</td>
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<td>Busulfan</td>
<td>Alkylating agent</td>
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<td>Seizures</td>
<td>Keratoconjunctivitis sicca Cataract blurred vision</td>
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<tr>
<td>Capecitabine</td>
<td>Pyrimidine antimetabolite</td>
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<td>Confusion, white matter changes</td>
<td>Decreased visual acuity Corneal opacities Keratitis</td>
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**continued**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>More Common Side Effect</th>
<th>Less Common Side Effect</th>
<th>Reported Ocular Toxicity</th>
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</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>Alkylating</td>
<td>Peripheral neuropathy</td>
<td></td>
<td>Optic neuropathy&lt;br&gt;Fibrosis of extraocular muscles with local injection&lt;br&gt;Orbital soft tissue inflammation&lt;br&gt;Periorbital edema&lt;br&gt;Eye pain&lt;br&gt;Conjunctival injection / chemosis&lt;br&gt;Corneal edema&lt;br&gt;Elevated intraocular pressure&lt;br&gt;Macular pigment changes / maculopathy&lt;br&gt;Optic neuropathy&lt;br&gt;Cortical visual loss&lt;br&gt;Blurred vision</td>
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<td>Carmustine</td>
<td>Alkylating</td>
<td>Encephalopathy</td>
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<td>Retinal ischemia&lt;br&gt;Eye pain&lt;br&gt;Conjunctival injection&lt;br&gt;Corneal edema&lt;br&gt;Corneal opacities&lt;br&gt;Elevated intraocular pressure&lt;br&gt;CRAO&lt;br&gt;Retinal vascular periarteritis&lt;br&gt;Optic disc edema&lt;br&gt;Fibrosis of extraocular muscles&lt;br&gt;Optic neuropathy&lt;br&gt;Blurred vision&lt;br&gt;Decreased visual acuity</td>
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<td>Chlorambucil</td>
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<td>Keratitis&lt;br&gt;Retinal hemorrhages&lt;br&gt;Optic disc edema&lt;br&gt;Diplopia</td>
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<td>Peripheral neuropathy&lt;br&gt;Lhermitte sign&lt;br&gt;Autonomic neuropathy&lt;br&gt;Ototoxicity&lt;br&gt;Vestibular toxicity&lt;br&gt;Muscle cramps</td>
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<td>Encephalopathy&lt;br&gt;Optic neuropathy&lt;br&gt;Retinopathy&lt;br&gt;Cortical visual loss&lt;br&gt;Homonymous hemianopia&lt;br&gt;Cavernous sinus syndrome&lt;br&gt;Orbital soft tissue inflammation&lt;br&gt;Uveal effusion&lt;br&gt;Macular / retinal pigment changes&lt;br&gt;Optic disc edema&lt;br&gt;VOR suppression&lt;br&gt;Thickening of extraocular muscles&lt;br&gt;Nystagmus&lt;br&gt;Dyschromatopsia&lt;br&gt;Blurred vision / decreased visual acuity</td>
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<td>Cladribine</td>
<td>Antimetabolite</td>
<td>Confusion&lt;br&gt;Headache&lt;br&gt;Neuropathy&lt;br&gt;Dizziness&lt;br&gt;Para / quadraparesis</td>
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<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>Encephalopathy&lt;br&gt;Seizures&lt;br&gt;Dizziness</td>
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<td>Blurred vision&lt;br&gt;Lacrimal duct stenosis&lt;br&gt;Epiphora&lt;br&gt;Keratoconjunctivitis sicca&lt;br&gt;Pupillary miosis&lt;br&gt;Cataract&lt;br&gt;Blurred vision</td>
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<th>Drug</th>
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<th>More Common Side Effect</th>
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<td>Arachnoiditis</td>
<td>Elevated intracranial pressure (more common with intrathecal therapy)</td>
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<th>Less Common Side Effect</th>
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<td>DNA polymerase inhibitor</td>
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<td>Dyschromatopsia</td>
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<td>Thromboembolism</td>
<td>Maculopathy / retinopathy</td>
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<td>Corneal opacities</td>
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<td>Optic neuropathy</td>
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<td>Retinal hemorrhages</td>
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<td>Cataract</td>
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<td>Decreased visual acuity</td>
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<td>Temozolomide</td>
<td>Alkylating agent</td>
<td>Headache</td>
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<tr>
<td>Thalidomide (Lenalidomide - more recent analog)</td>
<td>Immunomodulatory agent</td>
<td>Somnolence Peripheral neuropathy</td>
<td>Headache Tremor Less neurotoxicity with lenalidomide</td>
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<td>Thiotepa</td>
<td>Alkylating agent</td>
<td></td>
<td>Aseptic meningitis Myelopathy</td>
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<tr>
<td>Topotecan</td>
<td>Topoisomerase I inhibitor</td>
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<td>Headaches Paresthesias</td>
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*continued*
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**TABLE 1 continued**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>More Common Side Effect</th>
<th>Less Common Side Effect</th>
<th>Reported Ocular Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine</td>
<td>Microtubule inhibitor</td>
<td>Similar but lower rates of toxicity than vincristine</td>
<td>Peripheral neuropathy</td>
<td>Diplopia</td>
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<tr>
<td>Vincristine</td>
<td>Microtubule inhibitor</td>
<td>Peripheral neuropathy</td>
<td>Seizures</td>
<td>Blurred vision</td>
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<td>Autonomic neuropathy</td>
<td>Cranial neuropathy</td>
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<td></td>
<td>Ataxia</td>
<td>Including vocal cord</td>
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<td></td>
<td></td>
<td>Jaw pain</td>
<td>paralysis</td>
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<td>Headache</td>
<td>SIADH</td>
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**SITES OF INJURY / CLINICAL SYNDROME**

**Encephalopathy**

When given in high enough doses nearly all of the commonly used chemotherapy agents may cause encephalopathy. The clinical findings include confusion, disorientation, and abnormal behavior, and these findings are similar (and may be indistinguishable) to those of other causes of encephalopathy. The encephalopathy may be more diffuse and result in seizures, or may be more localized as in posterior reversible encephalopathy syndrome (PRES). Encephalopathy related to chemotherapy may be acute or chronic, when characterized by dementia and sometimes seizures. The dementia often causes patients to be withdrawn. A constellation of difficulties including memory loss, cognitive difficulties, and inattention has been termed “chemobrain”¹⁰, which some authors attribute more to the psychological effects of the cancer itself rather than to chemotherapy and treatment.² There may be progression of white matter changes in the brain years after treatment.

**Cerebellar syndrome**

Truncal and appendicular ataxia characterize a cerebellar syndrome most commonly associated with 5-FU and cytarabine. In some patients the cerebellar findings are reversible and in others they persist. Diffuse loss of Purkinje cells in the cerebellum has been noted. Vestibular type nystagmus has been reported in some patients with cerebellar dysfunction thought to be caused by chemotherapy.

**Neuropathy**

One of the most common neurologic toxicities of chemotherapy is peripheral neuropathy.¹¹,¹² It may be diffuse or focal.¹³ The diffuse form may occur acutely (suramin), with a sensorimotor pattern characterized more by motor weakness. It may be primarily sensory, with pain as a predominant symptom (cisplatin), and it may be more of a combination beginning with sensory paresthesias and progressing to weakness (vincristine).

Focal neuropathy (vincristine and cisplatin) is less common. Diplopia from ocular motor involvement has been a characteristic form of vincristine-induced neuropathy.
Optic neuropathy
Optic neuropathy has been reported in association with elevated intracranial pressure (cytarabine), due to anterior ischemic optic neuropathy (nitrosureas), from “optic neuritis”, and from toxic optic neuropathy. Many of these reports have confounding factors, including multiple drug therapy, and details are often omitted so that it is difficult to conclude whether the chemotherapeutic agent was the cause of the optic neuropathy.

Retinopathy
A number of types of retinopathy have been described. These include cystoid macular edema (mitotane), and macular pigmentary changes. The retinopathy may be ischemic (cisplatin and carmustine) with retinal vascular occlusions and/or cotton wool spots. There may be pigmentary changes (cisplatin). Splitting of the outer plexiform layer was noted on histopathology from a patient with an inadvertent overdose of intravenous cisplatin and persistent visual loss. Toxic retinopathy (tamoxifen) may cause decreased central vision.

External disease / dysfunction of the anterior segment
Dry eye syndrome with punctate epithelial changes may be particularly more common with 5-FU therapy. Keratitis, corneal opacities, and conjunctivitis are typically all managed conservatively with artificial tears. Lacrimal duct stenosis (docetaxel) may cause epiphora and may be averted with silicone tube intubation of the lacrimal duct system. An increase in cataract formation has been noted with several agents, including posterior subcapsular cataract with busulfan. Corneal ulceration may occur in association with dry eye syndrome and with an increased predisposition to infectious disease (herpetic keratitis).

Other neurologic findings
Myelopathy, most commonly from methotrexate, cytarabine, or thiota, hearing loss (cisplatin), and decreased sensation of smell and taste may occur with variable frequency and severity.

COMPLICATIONS OF SYSTEMIC CHEMOTHERAPY
Antimetabolites
These drugs interfere with production of nucleic acids by three mechanisms. Some inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for deoxyribonucleic acid (DNA) synthesis, thus inhibiting the replication process. Extended periods of inhibition of this process are usually cytotoxic. Others are substituted for purines or pyrimidines in the anabolic nucleotide pathways. Finally, some antimetabolites produce apoptosis—a form of programmed cell death—in susceptible cells. In some cases, more than one mechanism is responsible for the effects of the drug.

Methotrexate
The most widely used chemotherapeutic agent in cancer therapy, MTX is a competitive inhibitor of dihydrofolate reductase, an enzyme that reduces dihydrofolate to tetrahydrofolate. MTX blocks the synthesis of DNA, ribonucleic acid (RNA), and protein by limiting the availability of reduced folates. It is relatively water soluble with little penetration into the central nervous system (CNS) unless given intravenously in high doses, intrathecally, or with modification of the BBB.

MTX can be given orally, intravenously, intra-arterially, or intrathecally, although even at high doses, oral administration produces variable and incomplete absorption. Pemetrexed, similar to MTX, has not been noted to cause the same types of neurotoxicity. Methotrexate has also been injected into the vitreous for intraocular lymphoma and uveitis with macular edema.

Standard doses of oral MTX rarely cause neurotoxicity; however, the drug can cause toxicity when given either intravenously in high doses or intrathecally. The most common neurotoxicities are an acute or subacute encephalopathy, a chronic progressive leukoencephalopathy, and an acute meningitis.

An acute syndrome characterized by confusion, somnolence, disorientation, and seizures occurs in 25% of patients within 24 hours of high-dose MTX treatment. The subacute encephalopathy caused by MTX has an abrupt onset and typically occurs a few days to 20 days after the second to fourth course of the drug. It is characterized by seizures, confusion, hemiparesis, and coma. There may be diffuse slowing on the electroencephalogram (EEG), but neuroimaging reveals no abnormalities. The cerebrospinal fluid (CSF) may have a normal or increased concentration of protein, and MTX levels in both serum and CSF are in a therapeutic range.

A chronic delayed leukoencephalopathy may develop after either high dose intravenous or intrathecal treatment with MTX. It is usually gradual in onset with personality changes and intellectual decline as the initial manifestations. Progressive dementia, pseudobulbar palsy, hemiparesis, quadriaparesis, ataxia, focal seizures, and stupor may develop. The severity is variable, and the course may be static or progressive. MR imaging has shown lesions within the centrum semiovale and periventricular white matter consistent with leukoencephalopathy. Intrathecal MTX often causes an acute meningeal reaction. A less common complication of intrathecal MTX is a complete transverse myelopathy characterized by weakness and sensory loss. An intrathecal overdose of MTX can produce an ascending myelopathy and necrotizing leukoencephalopathy that may be fatal.

Ocular manifestations associated with high dose MTX therapy include periorbital edema, photophobia, eye pain and burning with keratitis, seborrhoeic blepharitis, conjunctivitis and decreased reflex tearing. Disruption of the blood retinal barrier increases ocular toxicity. Macular edema with pigmented changes in the foveal and parafoveal regions occurred when MTX was given with intravenous cyclophosphamide and mannitol.
Axonal degeneration and demyelination of the optic nerve and chiasm, with similar abnormalities in the brainstem and spinal cord, after treatment with intraventricular MTX via an Ommaya reservoir have been described. Optic disc edema and visual field defects were noted in a patient with psoriatic arthritis treated with oral MTX. The visual course was noted to vary with changes in the dosage of MTX. Optic neuropathy attributed to oral MTX has been described in patients with rheumatoid arthritis.

Bilateral internuclear ophthalmoplegia (INO) associated with ptosis occurred in a patient with mediastinal T cell lymphoma who received 2400 cGy of cranial irradiation, intrathecal MTX and cytarabine, and chemotherapy with vincristine, doxorubicin, prednisone, 6 mercaptopurine, and L asparaginase for CNS prophylaxis. See saw nystagmus developed in a patient who received radiation and intrathecal MTX for central nervous system lymphoma. The authors noted that nystagmus developed without evidence of a brainstem lesion on MR imaging.

5-Fluorouracil (5-FU) is a fluorine substituted analog of the pyrimidine uracil. It is an antimetabolite that inhibits thymidylate synthetase, blocking DNA synthesis by reducing the formation of thymidine monophosphate. It is also incorporated into RNA and specifically inhibits the S phase of the cell cycle.

5-FU is usually given intravenously by short infusions or bolus injection, but the drug can be given intra arterially, by direct injection, or topically. Elimination is through metabolism, primarily by the liver.

5-FU readily crosses the BBB and thus may be toxic to the CNS, with accumulation in the cerebellum. The mechanism of neurotoxicity is unknown but believed to be related to accumulation of 5-FU degradation products, such as fluorocitrate, which inhibit the Krebs cycle. Neurotoxicity is rare with conventional doses of 5-FU, except in patients with a congenital abnormality of pyrimidine metabolism who develop ataxia at low doses. Capecitabine (Xeloda), a 5-fluorouracil prodrug, has a similar side effect profile and has been reported to cause trismus and neuromuscular symptoms. Corneal deposits and ocular irritation have also been noted.

The most common neurotoxicity associated with 5-FU is a subacute cerebellar syndrome. It is characterized by gait and limb ataxia, dysarthria, and nystagmus. The syndrome begins hours to days after drug administration and reverses 1–6 weeks after stopping the medication. From 25 to 50% of patients who receive systemic 5-FU have ocular complications. Conjunctival irritation and blepharitis are the most common. Periorbital edema, ocular pain, photophobia, eyelid dermatitis with cicatricial ectropion, ankyloblepharon, and lid necrosis after lid cryotherapy can also occur. Cataracts may develop, and the incidence of cataract is increased in patients who receive RT along with 5-FU. Excess lacrimation occurs in up to 50% of patients who receive 5-FU. The tearing develops gradually and subsides after treatment is discontinued.

The most common neuro ophthalmic manifestation of 5-FU toxicity is nystagmus, which usually occurs in the setting of the subacute cerebellar syndrome. The nystagmus is gaze evoked and resolves after the dose of 5-FU is lowered or the drug is stopped.

Two patients treated with 5-FU for colon cancer developed both convergence and divergence insufficiency during treatment. The authors postulated that the ocular motor dysfunction in these patients was caused by fluorocitrate toxicity to the brainstem. Bilateral oculomotor nerve palsies have been noted in a patient treated with 5-FU.

A case of "retrobulbar neuritis" was reported after intra arterial injections of cisplatin and 5-FU into the left lingual artery for squamous cell carcinoma of the left tonsillar fossa. The authors postulated an inflammatory rather than a vascular cause; however, the ipsilateral optic nerve and hemispheric complications suggest a direct toxic effect of the chemotherapy or posterior ischemic optic neuropathy.

Acute, recurrent, toxic optic neuropathy can be caused by 5-FU. A patient with bilateral asymmetric optic neuropathy with disc swelling was seen in a patient on continuous IV 5-FU therapy. A dihydropyrimidine dehydrogenase (DPD) deficiency was documented which increases risk for 5-FU toxicity. Indeed, systemic and neurologic toxicity can be much worse in patients with DPD deficiency, which is inherited in an autosomal recessive manner and occurs in 3% of cancer patients.

As with systemic toxicity, the neuro ophthalmologic toxicity of 5-FU is related to the route of administration and other co existing therapies. When combined with surgery and RT, regional infusion of 5-FU with catheter introduction through the superficial temporal artery for carcinoma of the paranasal sinuses resulted in visual loss in nine of 57 patients in one report and in four of 23 patients in another. The ocular cause of visual loss was not described, but in each case, the eye was in the field of radiation.

A patient with diplopia, deafness, ataxia, and confusion was diagnosed with Wernicke’s encephalopathy 11 days after initiation of a 4 week treatment of continuous infusion of 5-fluorouracil and low-dose cisplatin. The authors suggested that 5-FU/cisplatin toxicity may manifest as Wernicke's encephalopathy when associated with intravenous hyperalimentation and thiamine deficiency.
Gemcitabine
Autonomic neuropathy and posterior leukoencephalopathy\textsuperscript{47,48} have been described with gemcitabine, a cytosine analog.

Cytosine Arabinoside
Cytosine arabinoside (cytarabine, ara-c) is a sugar–modified analog of the pyrimidine, s cytidine. Ara-c acts on proliferating cells as an S–phase specific cytotoxic agent. It inhibits DNA polymerase and also inhibits DNA synthesis by becoming incorporated into DNA. It is given intravenously in continuous infusion over days, in high–dose regimens, or intrathecally for the treatment or prophylaxis of CNS leukemia or lymphoma.

At conventional doses, ara-c does not cross the BBB well, and there is thus little neurotoxicity.\textsuperscript{17} However, a cerebellar syndrome, encephalopathy, and peripheral neuropathy have been described.

Approximately 10% of patients receiving high dose ara-c develop a severe cerebellar syndrome\textsuperscript{2,3} and cerebellar dysfunction is the major dose limiting toxicity of ara-c. The early symptoms include nystagmus, dysarthria, and appendicular and gait ataxia.\textsuperscript{2} MR images may reveal extensive cortical and subcortical white matter brain edema.\textsuperscript{49} An acute demyelinating polyneuropathy or other peripheral neuropathy can develop in patients who are treated with high dose intravenous ara-c. Aseptic meningitis occurs in about 10–20% of patients following intrathecal or intraventricular treatment with ara-c. Myelopathy with paraplegia or cauda equina syndrome may also occur after intrathecal administration of this drug. Intrathecal administration of ara-c is occasionally associated with seizures or an encephalopathy that may be extremely severe. Ocular toxicity from ara-c most often consists of keratoconjunctivitis, which is characterized by superficial punctate epithelial defects, subepithelial granular deposits, central punctate opacities, refractile microcysts, mild stromal edema, and striae in Descemet’s membrane.

As noted above, a cerebellar syndrome occurs as a toxic effect of ara-c, and this is often characterized in part by a gaze evoked nystagmus.

Bilateral subacute progressive optic neuropathy developed in two patients during remission of acute lymphoblastic leukemia, both beginning 8 months after initiation of treatment.\textsuperscript{50} Another report of visual loss after high–dose cytosine arabinoside noted bilateral optic disc edema.\textsuperscript{51} Optic disc edema attributed to cytarabine–induced elevated intracranial pressure developed in a patient with acute myeloblastic leukemia.\textsuperscript{52} The causative mechanism was unclear and the optic disc swelling resolved with acetozolamide and prednisone.

A patient with bilateral abducens nerve pareses was reported.\textsuperscript{53} The authors believed that the timing of the abducens nerve pareses and the association with a cerebellar syndrome supported the notion that ara-c was responsible.

Purine Analogs
The purine analogs include fludarabine, cladribine, and pentostatin. Fludarabine causes competitive inhibition of replicative DNA polymerases, is incorporated into nascent DNA, and is also an effective DNA chain terminator. It is also incorporated into RNA, thus inhibiting transcription.\textsuperscript{73} Fludarabine can be administered via a single intravenous bolus or by continuous infusion.

In low doses, there is little neurotoxicity from the purine analogs, although fludarabine may cause transient somnolence or peripheral neuropathy.\textsuperscript{54} In addition, some patients develop reversible, focal neurologic signs. MR imaging in such patients reveals areas of hyperintensity on T2–weighted images.\textsuperscript{17}

Patients who are given high doses of fludarabine can experience a delayed progressive encephalopathy characterized by cortical blindness, dementia, coma, and, eventually, death.

Pentostatin can cause a dose related encephalopathy, sometimes with seizures and coma. It is uncommon at the usual doses of the drug, however.

Ocular toxicity from the purine analogs is rare. Individual case reports describe conjunctivitis, keratitis, eye pain, blepharitis, cataract, and retinal detachment. Neuroophthalmologic complications include visual loss, sometimes from an unclear mechanism. Some patients have been noted to have an optic neuropathy, “optic neuritis”, and cerebral visual loss. Retinopathy has been described with fludarabine.\textsuperscript{54} A patient with visual loss, felt to be related to toxic optic neuropathy, has been described from cladribine.\textsuperscript{55}

Pyrimidine Analogs
Bromodeoxyuridine (BUdR) is a halogenated pyrimidine analog that is incorporated into DNA in a competitive manner in place of thymidine during DNA replication. Ocular complications have included eyelid erythema and induration, conjunctival chemosis and hyperemia, conjunctivitis, dry eye syndrome, ectropion of the eyelids, and exposure keratitis.

Hydroxyurea
Hydroxyurea is an antimetabolite that inhibits ribonucleotide reductase, an enzyme that is involved in the de novo synthesis of all precursors used in DNA synthesis and that converts ribonucleoside diphosphates to deoxyribonucleotide diphosphates. Neurotoxicity related to treatment with hydroxyurea is rare. Nevertheless, some patients experience headache, dizziness, disorientation, drowsiness, and seizures. Ocular pain is occasionally reported in patients taking hydroxyurea.\textsuperscript{56}

Alkylation Agents
Alkylation agents cause linking of nucleic acids, resulting in cross–linking between DNA strands, between bases in the same DNA strand, or within a monoalkylated DNA guanine unit. Although these agents are cell cycle phase–nonspecific, the biologic consequences are more
severe when alkylation occurs during DNA synthesis. Alkylating agents may also cause apoptosis in sensitive cells.

Alkylating agents are teratogenic, mutagenic, and carcinogenic, the most common secondary malignancy being acute leukemia. The nitrogen mustards include mechlorethamine, chlorambucil, cyclophosphamide, and ifosfamide.

Hearing loss and encephalopathy can occur in patients receiving nitrogen mustards in conventional intravenous doses. Intracarotid infusions of nitrogen mustards can cause seizures, hemiplegia, coma, and death.

Intracarotid infusion of nitrogen mustard may cause a severe ipsilateral necrotizing uveitis that can progress to retinal and choroidal atrophy.

Patients receiving intracarotid nitrogen mustards can develop a transient ipsilateral ophthalmoplegia. 18

**Procarbazine**

Procarbazine is a hydrazine derivative. It is a weak monoamine oxidase inhibitor that acts primarily as an alkylating or methylating agent. It is administered orally because intravenous administration has unacceptable neurotoxicity.

Encephalopathic changes ranging from mild drowsiness to stupor and reversible ataxia have been noted. 2 Distal paresthesias occur uncommonly with procarbazine. The neurologic examination in such patients may be normal or show depressed deep tendon reflexes.

Rare ocular side effects of procarbazine include photophobia, keratitis, “inability to focus”, and retinal hemorrhage. 7 These usually resolve once the drug is stopped.

Papilledema, photophobia, diplopia, and nystagmus are also said to occur in some patients treated with procarbazine, but the authors of these anecdotal reports provide no specific details.

**Dacarbazine**

Dacarbazine is a drug that methylates both DNA and RNA. Neurotoxicity is rare in patients being treated with dacarbazine. Nevertheless, seizures, encephalopathy, and dementia have all been described in individual patients. 2

**Chlorambucil**

Chlorambucil is an alkylating agent with immunosuppressive activity. The drug is administered in daily oral doses.

Neurotoxicity does not occur from standard doses of chlorambucil. However, encephalopathy with seizures, including myoclonic seizures, can occur with accidental drug overdose.

Chlorambucil rarely causes ocular toxicity. Some patients develop a mild superficial keratitis.

Optic disc edema has been reported. Visual hallucinations apparently occurred in a patient receiving chlorambucil.

**Busulfan**

Busulfan (Myleran) is an alkylating agent used orally.

Busulfan crosses the BBB easily. When high doses of the drug are given in preparation for BMT, seizures commonly occur. 2 The seizures usually begin 2–4 hours after the dose is given and thus can be prevented with anticonvulsants.

Tremor, encephalopathy with drowsiness, agitation and hallucinations, followed by multiple organ failure, coma and death have been described. A myasthenic syndrome during treatment with busulfan for CML has been noted. 17

A well described ocular toxicity related to busulfan is the development of cataracts. 7 The typical cataract develops in the posterior subcapsular region in months to years after therapy. The incidence of cataract increases with both duration and total dose. The appearance of the cataract is identical with that seen with aging or after chronic treatment with systemic corticosteroids. The mechanism of cataract formation is postulated to be decreased DNA synthesis in lens epithelium. Keratoconjunctivitis sicca (KCS) rarely occurs with busulfan. It is treated with ocular lubricants.

**Cyclophosphamide**

Cyclophosphamide (Cytoxan), is a modified nitrogen mustard that requires activation by the liver. It is given orally or intravenously.

Transient blurring of vision has been noted, lasting from 1 hour to 2 weeks and occurring within 24 hours after the onset of treatment. KCS occurs in 50% of patients receiving cyclophosphamide and lasts up to 2 weeks. Rarely, cataracts and blepharoconjunctivitis occur. 7

Macular pigmentary changes occurred in a patient treated with cyclophosphamide, MTX, and mannitol. 24

Optic neuropathy has been described in patients receiving cyclophosphamide. Transient miosis occurs in some patients treated with cyclophosphamide. 57 This may be caused by a parasympathomimetic effect of the drug.

**Ifosfamide**

Ifosfamide is an alkylating agent similar to cyclophosphamide.

Unlike cyclophosphamide, ifosfamide is associated with severe but often reversible neurotoxicity. 58 An encephalopathy 59 develops in 20% of patients who are treated with ifosfamide, usually within hours but occasionally after 4–6 days of therapy. Findings may include disorientation, confusion, somnolence, hallucinations, tremors, ataxia, aphasia, weakness, seizures, extrapyramidal deficits, and cranial neuropathies. All neurologic deficits usually resolve within 3 days of completing therapy, but they may persist, and occasional fatalities and cerebral atrophy may occur.

Isolated case reports indicate that some patients who are treated with ifosfamide develop transient blurred vision and conjunctival hyperemia. 7
Nitrosoureas
The nitrosoureas include BCNU (carmustine), CCNU (lomustine), methyl-CCNU (semustine), PCNU, ACNU, streptozotocin and chlorozotocin. Their lipophilic properties, small molecular weight, and limited binding to plasma proteins contribute to blood–brain barrier penetration. When BCNU is delivered by intracarotid infusion, the level of drug that reaches the tumor is four times the dose that would normally be delivered intravenously. This same dose also reaches the brain, eye, and ocular adnexa. Implantation of chemotherapy containing polymers, including BCNU, has been used in high-grade astrocytic neoplasms and for paraspinal tumors.

There is little neurotoxicity from the nitrosoureas when they are given in the usual intravenous dosage. High-dose intravenous BCNU when combined with autologous BMT can produce an encephalopathy and leukoencephalopathy characterized by confusion and seizures. Cerebral edema may occur with wafer therapy. High-dose intravenous therapy with the nitrosoureas causes mild, nonspecific ocular manifestations, such as conjunctival hyperemia and nonspecific blurred vision. In addition, nerve fiber layer infarction has been described.

Intracarotid therapy accounts for the majority of neurologic toxicity of the nitrosoureas. Focal seizures or transient confusion occur in patients during or shortly following intracarotid infusion of BCNU. Intracarotid infusion may also cause a severe ipsilateral encephalopathy characterized by seizures, hemiparesis, and progressive focal neurologic deficits. Necrosis, pathologically similar to radiation necrosis, also occurs, and concurrent RT provides an additive effect.

In contrast to intravenous treatment, intracarotid injection of BCNU, with or without concomitant intracarotid cisplatin can be associated with severe visual complications, probably from ischemia, perhaps from endothelial toxicity. Delayed, severe, ipsilateral neuroretinal toxicity, CRAO, and retinal vasculitis have been described. Optic disc edema suggestive of anterior ischemic optic neuropathy has been described (AION). The authors suggested the optic neuropathy in this patient was caused by a toxic vasculitis. Other presumably ischemic complications have included homonymous hemianopia and orbital and ocular pain.

Increased orbital vascularity, vasodilation, arteriovenous shunting, and glaucoma secondary to orbital congestion are occasional complications of intracarotid infusion of the nitrosoureas. Vitreous opacification, conjunctival hyperemia, corneal edema, and corneal opacities also may occur. These effects can be diminished by supra-ophthalmic infusion of the drug.

Optic neuropathy, in association with myelopathy and branch retinal artery occlusion, has been noted with high dose intravenous BCNU, cisplatin and autologous bone marrow transplant. Optic neuropathy and orbital complications, most likely from ischemia, may occur in patients who receive BCNU via intracarotid infusion.

Cisplatin
Cisplatin (Cis-diamminedichloroplatinum) is a heavy metal alkylating agent that probably acts by binding DNA, thus forming interstrand and intrastrand cross–links that interfere with DNA synthesis and transcription. The drug can be administered intravenously or locally. Intra-arterial infusion may result in more severe ototoxicity.

Two types of neurotoxicity are dose–limiting for cisplatin treatment: ototoxicity and peripheral neuropathy. The ototoxicity occurs at the level of the cochlea, with extensive loss of outer hair cells and occasional loss of inner hair cells. Vestibular toxicity, in contrast to ototoxicity, is rarely seen with cisplatin therapy. It is characterized by vertigo and oscillopsia and may occur with or without concurrent ototoxicity.

The peripheral neuropathy that occurs as a complication of cisplatin therapy is primarily a large–fiber sensory neuropathy, thought to occur from injury to the dorsal root ganglion, and begins with distal paresthesias, often progressing for months after discontinuing the medication until the patient has a disabling sensory ataxia.

Encephalopathy may occur after intravenous infusion of cisplatin. It is characterized by seizures, cortical blindness, and focal neurologic deficits.

Abnormal color perception has been described. Retinal toxicity frequently occurs after intracarotid injection of cisplatin. Splitting of the outer plexiform layer was noted on histopathology from a patient with an inadvertent overdose of intravenous cisplatin and persistent visual loss. The histopathologic findings were consistent with loss of the b–wave on ERG. The risk of retinal toxicity is increased with intra-arterial therapy.

A maculopathy characterized by decreased visual acuity, central scotoma, and retinal pigment epithelial loss and clumping occurred in three of eight patients who received monthly ipsilateral infra-ophthalmic cisplatin.

Transient cerebral blindness is a common complication of cisplatin therapy. It may develop with or without evidence of clinical encephalopathy.

Cisplatin–related visual loss occurs from causes other than damage to the postgeniculate visual sensory pathway. Optic nerve dysfunction also occurs in patients treated with cisplatin. Some cases are called “optic neuritis,” although there is no evidence that the pathogenesis of the visual loss is inflammatory. Others are more appropriately called toxic optic neuropathies. Papilledema has been described in some patients receiving cisplatin. Although supra-ophthalmic injection of cisplatin diminishes the risk of ocular toxicity from intra-arterial administration, it does not eliminate the risk of visual loss or orbital toxicity.
Carboplatin
Carboplatin, a platinum analog of cisplatin with similar activity, is used to treat recurrent brain tumors and optic pathway gliomas in children and retinoblastoma, with less neurotoxicity than cisplatin. Ocular toxicity includes retinopathy after intra arterial infusion. Limitation of extraocular movements was seen in 12 eyes of 10 patients treated with subtenon carboplatin as part of multimodality therapy for retinoblastoma. Histopathology suggested fat necrosis was partly responsible for the mechanical restriction of the limitation of ductions. Cerebral blindness from carboplatin has been reported.

Oxaliplatin
Oxaliplatin is a platinum compound used in the treatment of colorectal cancer. Peripheral neuropathy may occur in 10–15% of patients, and is less severe than that due to cisplatin. Acute neurotoxicity occurs within 1 hour of infusion and includes cold–exacerbated paresthesias, jaw and eye pain, ptosis, and cramps, which may mimic neuromyotonia.

Thiotepa
Thiotepa is a drug with a mechanism of action similar to that of the nitrogen mustards. Back pain and myelopathy have been described. Topical use of thiotepa can cause both keratitis and conjunctivitis. Eyelid depigmentation can also occur and is probably enhanced by exposure to sunlight.

Temozolamide
Temozolamide is an alkylating agent with the ability to penetrate the BBB. It may cause headaches and increases the risk of vasogenic edema when combined with radiation therapy.

Antibiotics
The antimicrobials mostly have a chemotherapeutic effect by noncovalent DNA binding, resulting in untwisting of the double helix, intercalation, and impairment of template synthesis.

Anthracycline Antibiotics
The anthracycline antibiotics include doxorubicin, daunorubicin, and idarubicin. All are administered intravenously.

Doxorubicin, daunorubicin, epirubicin, and mitoxantrone can all produce a severe myelopathy and encephalopathy if they are accidentally injected intrathecally. In addition, TIAs or cerebral infarction may occur from cardiac thrombi associated with doxorubicin cardiac toxicity, and cerebral necrosis and hemorrhagic infarcts can also occur after intracarotid injection of doxorubicin and similar agents combined with osmotic BBB modification.

Conjunctivitis occurs in some patients treated with doxorubicin, particularly during and shortly after infusion. Increased lacrimation may persist for days. Periorbital edema and mild facial edema occurred in one patient who received doxorubicin and cyclophosphamide. The edema resolved over time but recurred with a second treatment.

Mitoxantrone causes a blue green discoloration of the sclera. The discoloration has no visual significance.

The neuro ophthalmologic toxicity of the anthracycline antibiotics is not clear, because most of the patients with complications of neuro ophthalmologic interest have also been treated with other chemotherapeutic agents. Blepharospasm, along with photophobia and ocular itching occurred in a patient treated with doxorubicin, cyclophosphamide, and high dose tegafur (furanyl 5–FU). The blepharospasm coincided with the courses of treatment and resolved after completion of therapy. A direct irritation of sensory nerve endings or CNS involvement from the combination of agents was proposed as the mechanism for these manifestations.

Mitomycins
The mitomycins are derived from the streptomyces species. Mitomycin C is an alkylating agent that cross–links DNA.

With ophthalmic use, signs of irritation of the eyelids, conjunctiva, cornea, and sclera occur. These are usually short–lived, however, lasting only a few weeks. More serious, immune–mediated responses include corneal and scleral necrosis and melting that mimics scleromalacia perforans or necrotizing scleritis. Antimetabolites used during filtering surgery increase the risk of postoperative bleb leaks, hypotony maculopathy, and endophthalmitis.

Bleomycin
Bleomycin is a water–soluble glycopeptide antibiotic that causes a block in the early G2 phase of the cell cycle and inhibits DNA synthesis. It is most commonly used intravenously or intramuscularly. Neurotoxicity is unusual with bleomycin, but it has been reported to cause cerebral infarction when used in combination with cisplatin.

Mithramycin
Mithramycin (plicamycin) is an antibiotic that binds DNA and inhibits both DNA and RNA synthesis. Mithramycin can also cause headache, irritability, lethargy, and weakness. It is not associated with any significant ocular or neuro ophthalmologic complications, but it may cause headaches.

Suramin
Dose–limiting neurotoxicity, including polyneuropathy, remains the most serious complication of suramin treatment. A symptomatic keratopathy, with foreign body sensation and corneal epithelial deposits, may occur.

Vinca Alkaloids
The vinca alkaloids, vincristine and vinblastine, are derived from the periwinkle plant. They bind to tubulin, prevent microtubular formation, and arrest cells in metaphase. Other semi–synthetic compounds, such as vindesine and vinorelbine have been developed with similar modes of action.

A symmetric dose limiting sensorimotor peripheral neuropathy occurs in nearly all patients who receive repeated doses of vincristine. A concomitant autonomic
neuropathy may also occur. The neurotoxicity is both age and dose dependent, and the symptoms may unmask and be more severe in some forms of hereditary neuropathy such as Charcot–Marie–Tooth disease. Encephalopathy and seizures occasionally occur in patients treated with the vinca alkaloids. Death may occur with inadvertent intrathecal administration.

Cranial neuropathies often occur in the setting of a vincristine induced peripheral neuropathy. The ocular motor nerves may be affected singly, particularly the abducens nerve, or in combination. Facial nerve paresis may also occur as an isolated phenomenon or in association with other cranial neuropathies. Up to 50% of patients treated with vincristine develop single or multiple cranial neuropathies, including ocular motor nerve palsies, resulting in ptosis and diplopia, at some point during their treatment. Visual hallucinations have rarely been reported with vincristine therapy.

**Taxoids**

Paclitaxel (Taxol) and docetaxel (Taxotere) are diterpene alkaloids or taxoids. They bind tubulin, causing the formation of large bundles of disordered microtubules.

Both Paclitaxel and docetaxel cause a predominantly sensory neuropathy involving large and small fibers and characterized by paresthesias, dysesthesias, and diminished deep tendon reflexes. Non-leaking cystoid macular edema occurred 2 months after the initiation of docetaxel in a patient with breast cancer. The symptoms spontaneously improved after discontinuing the docetaxel. Epiphora from canalicular stenosis caused by docetaxel may be avoided by early bicanalicular silicone intubation.

Cystoid macular edema has been described in relation to paclitaxel therapy. A sensation of light flashing across the visual field was reported by six patients during paclitaxel infusion.

**Mitotane**

Mitotane (P–DDD) is a direct suppressant of the adrenal cortex, via toxicity to mitochondria, and modifies peripheral steroid metabolism. It is administered orally.

Lethargy, somnolence, ataxia, and dizziness occur in a large percentage of patients treated with mitotane. In addition, cranial and peripheral neuropathies apparently occurred in a small percentage of patients.

A “toxic retinopathy” characterized by optic disc swelling and retinal hemorrhages has been described. A toxic neuroretinopathy developed in three of 19 patients receiving mitotane. The patients apparently developed retinal edema, intraretinal hemorrhages, and optic disc swelling, but specific details of the examinations were not provided by the authors. Abnormal electroretinography with retinal pigmentary changes and macular edema, perhaps related to mitotane–induced hypoadrenalism, have been described in a 32 year–old woman, whose vision improved after the medication was discontinued.

**HORMONES**

**Steroid Antagonists**

Tamoxifen (Nolvadex) and toremifene citrate (Fareston) are nonsteroidal estrogen antagonists that bind competitively to cytoplasmic estrogen receptors, arresting the cell in the G1 phase of the cell cycle. Tamoxifen is structurally similar to drugs with well–described ocular toxicity, such as chloroquine, chlorpromazine, and thioridazine. Aminoglutethimide, anastrozole (Arimidex), and letrozole (Femara) are nonsteroidal inhibitors of aromatase, and block the synthesis of steroid hormones. Nilutamide (Nilandron) is a nonsteroidal anti-androgen. Danazol (Danocrine), Goserelin (Zoladex), and leuprolide (leupron) are gonadotropin inhibitors.

Rare neurologic side effects of tamoxifen include a reversible encephalopathy, depression, headache, cerebellar dysfunction, and radiation recall syndrome.

The ocular toxicity with tamoxifen includes corneal and retinal dysfunction, particularly with high doses. Superficial corneal opacities with whorl–like opacities, and retinal deposits may cause blurred vision. Ophthalmoscopy revealed white refractile opacities in the perimacular area, macular edema, and punctate areas of retinal pigment epithelium depigmentation.

With standard doses of tamoxifen of 20 mg/day, some authors report no ocular toxicity, whereas others describe both retinal and corneal changes.

Nilutamide may cause symptomatic impairment of dark and light adaptation.

Optic disc edema has been described in patients taking tamoxifen. Leuprolide has been purported to cause unilateral optic disc edema from elevated intracranial pressure, which resolved 6 months after the discontinuation of treatment.

**MISCELLANEOUS DRUGS**

**Retinoids**

A physiologic approach to arresting or reversing carcinogenesis includes treatment with retinoids, such as Vitamin A (retinol) and its synthetic and naturally occurring analogs.

Some patients being treated with retinoids become depressed or psychotic. The mechanism by which this occurs is unknown.

Ocular side effects of retinoids include conjunctivitis and corneal opacities. Fenretinide can cause a reversible xerophthalmia and nyctalopia at high doses.

Patients treated with retinoids can develop hypervitaminosis A. This, in turn, can cause increased ICP, which typically resolves with normal vitamin A levels. Elevated ICP has also been noted in patients treated with all–trans–retinoic acid.
Topoisomerase inhibitors
The topoisomerase inhibitors include amsacrine, camptothecin, and the epipodophyllotoxins, VP–16 (etoposide) and VM–26 (teniposide). VP–16 inhibits chromatin function by inhibiting topoisomerase, thus delaying DNA replication. It is usually given orally or intravenously, but it can also be delivered intraperitoneally, intrapleurally, or by intracarotid infusion.

VP 16 may cause seizures, confusion, and somnolence when used in high doses in patients after BMT. It occasionally causes a reversible peripheral neuropathy. Amsacrine can also cause a transient peripheral neuropathy or seizures.

Thalidomide
Thalidomide was originally developed as a sedative and was found to be teratogenic, and withdrawn by the Food and Drug Administration (FDA). As part of an embryopathy, thalidomide has been associated with the brainstem syndrome of Möbius. Seizures and peripheral neuropathy have been reported.

Bisphosphonates
Pamidronate and zoledronic acid are bisphosphonates used in the treatment of hypercalcemia related to malignancy. Uveitis and scleritis have been reported as early (within 48 hours of treatment) side effects of pamidronate therapy.

L–asparaginase
L–asparaginase is an enzyme that catalyzes the hydrolysis of L–asparagine to aspartic acid and ammonia, thus depleting asparagine and decreasing protein and glycoprotein synthesis.

L–asparaginase can cause both an acute and a delayed encephalopathy. It develops within the first days of treatment as lethargy, disorientation, confusion, and seizures. It then spontaneously resolves. The delayed encephalopathy occurs about 1 week after treatment is begun. Reversible posterior leukoencephalopathy has been described.

The pathogenesis of neurotoxicity of L–asparaginase is probably metabolic, via the production of ammonia compounds, which can cross the BBB. Because L–asparaginase causes alterations in clotting factors, it can produce a coagulopathy that can lead to hemorrhage or thrombosis. Intracranial complications thus include lobar intracerebral hemorrhage, subcortical hemorrhage, superior sagittal sinus thrombosis, and cerebral infarction.

L–asparaginase has been reported to cause intracranial hypertension by virtue of its potential to cause thrombosis of the superior sagittal sinus, lateral sinus, or cortical veins.

Complications of local infusion
Some chemotherapeutic agents are used locally, and have been reported to be more likely to cause some side effects. Intraventricular methotrexate has been reported to cause cerebral edema and necrosis. A focal lumbosacral plexopathy has been noted after infusion of cisplatin in the iliac arteries. Cisplatin and carboplatin have been reported to cause an optic neuropathy and orbital toxicity after intracarotid infusion, possibly through an ischemic mechanism. Likewise, intracarotid infusion of BCNU has been reported to cause optic neuropathy, again thought to be caused by ischemia. Intracarotid infusion of doxorubicin has been reported to cause cerebral infarction and death.

Subtenon carboplatin may result in ocular motility abnormalities. Topical 5–FU predisposes to bleb leaks and infection after filtering surgery for glaucoma. Local therapy with Cilaidel wafers (with BCNU) may achieve tissue concentrations of 1000 times that of intravenous infusion and has been reported to cause cerebral edema, wound infection, and cerebrospinal fluid leak.

Complications of intrathecal therapy
Methotrexate and cytarabine are the most commonly used intrathecal agents (others include Thiotepa and an injectable, liposomal formulation of cytarabine). An aspetic meningitis may occur with administration of these agents intrathecally. With methotrexate this side effect may occur in 10% of patients. Cerebrospinal fluid may show pleocytosis. DepoCyt, a liposomal form of cytarabine, which requires less frequent administration, may be more likely to cause this toxicity. The syndrome appears to resolve spontaneously. Some authors recommend the addition of corticosteroids in attempts to decrease the risk of this form of chemical meningitis. Optic disc edema with elevated intracranial pressure has been noted in patients treated with intrathecal therapy, perhaps secondary to the chemical meningitis.

A less common, but severe, reaction has been described including life threatening encephalopathy and spinal cord lesions, including transverse myelopathy, after intrathecal therapy with both methotrexate and cytarabine. Histopathology has revealed demyelination and white matter vacuolization. In some patients the clinical findings related to myelopathy persist despite stopping therapy.

Combination effects of chemotherapy and radiation
Chemotherapy agents have been used in efforts to augment the effects of radiation in some patients. Because the mechanism of action of radiation therapy may be different than that of a selected chemotherapeutic agent, there may be biological cooperation, enhancement of cytotoxicity, and temporal modulation. However, some agents may be particularly more likely to cause toxicity in association with radiation therapy (Table 2), and these agents are thought to increase the toxicity of radiation when given in combination with radiotherapy. In particular, methotrexate, when given preirradiation appears to be less toxic than when given concurrently with radiation therapy or postirradiation, when the rate of leukoencephalopathy is much higher. Radiation recall, a phenomenon whereby a chemotherapy agent causes a cutaneous reaction (sometimes with myositis) in an area previously treated with radiation therapy, may be suggestive of the site of prior radiation ports.
TABLE 2: CHEMOTHERAPEUTIC AGENTS THOUGHT TO BE MORE LIKELY TO BE ASSOCIATED WITH NEUROTOXICITY WHEN COMBINED WITH RADIATION THERAPY.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Ototoxicity</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Leukoencephalopathy, Cognitive impairment, Pontine white matter changes</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Methylene blue and thiamine may reverse encephalopathy</td>
</tr>
<tr>
<td>Methotrexate (particularly when radiation therapy precedes methotrexate)</td>
<td>Leukoencephalopathy, Microangiopathy, Cognitive impairment, Myelopathy</td>
</tr>
<tr>
<td>Nitrosureas</td>
<td>Leukoencephalopathy, Cognitive impairment, Myelopathy</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>Increased vasogenic edema around tumor</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Myelopathy, Peripheral neuropathy</td>
</tr>
</tbody>
</table>

Portions of this table adapted with permission from: Choy H, Kim DW. Chemotherapy and irradiation interaction. Semin Oncol. 2003;30: (Suppl 9) 3-10.

Measures to limit toxicity from chemotherapy
Ocular ischemic syndromes may be less frequent if intra-arterial catheters are advanced beyond the ophthalmic artery, although some authors feel this may be a risk factor for stroke. Thus far, attempts at finding neuroprotective agents have been generally unsuccessful (Table 3). The use of artificial tears and topical lubricants is an easily employable strategy for those more likely to develop keratitis and dry eye syndrome. Silicone intubation of the lacrimal system may prevent ductal stenosis in patients taking docetaxel.

TABLE 3: INTERVENTIONS WHICH MAY HELP MITIGATE AGAINST CHEMOTHERAPY-INDUCED NEURO-OPTHALMIC SIDE EFFECTS.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Suggested Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>General consideration for agents causing peripheral neuropathy</td>
<td>Infusion of calcium and magnesium for oxaliplatin may be helpful but may limit tumor therapy. Sodium channel blockers, carbamazepine may help for oxalipatin. Amifostine without clear benefit for cisplatin neurotoxicity – may cause hypotension. Vitamin E may be helpful for cisplatin. Acetyl-L-carnitine may be helpful for cisplatin. Gabapentin and pregabalin may help relieve pain from neuropathy.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Advance infusion catheter beyond the ophthalmic artery for intracarotid administration. Screening for family history of peripheral neuropathy (Charcot Marie Tooth).</td>
</tr>
<tr>
<td>Carmustine / BCNU</td>
<td>Advance infusion catheter beyond the ophthalmic artery for intracarotid administration</td>
</tr>
<tr>
<td>Cytosine arabinoside</td>
<td>Artificial tears / 2-deoxycytidine drops prior to therapy</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Artificial tears prior to therapy. Possible screening tests for dihydropyrimidase dehydrogenase deficiency</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Artificial tears, folinic acid rescue therapy</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Carbamazepine may help neuropathy and neuromyotonia-like syndrome</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Silicone intubation of canalicular system</td>
</tr>
</tbody>
</table>

A number of agents have been used to try and mitigate against peripheral neuropathy in patients treated with chemotherapy; however, none have been proven definitively useful.13,94

CME ANSWERS
1. D
2. A
3. B


REFERENCES


LEARNING OBJECTIVES
1. To describe the clinical features of radiation-induced damage to the ocular motor system.
2. To review the pathophysiology of these disorders.
3. To highlight the features that aid in differential diagnosis of eye movement abnormalities following radiation therapy.

CME QUESTIONS
1. Diplopia, nystagmus and ataxia occurring 2 months after cranial irradiation is most likely due to which of the following:
   a. Stroke
   b. recurrent tumor
   c. brainstem demyelination
   d. pontine hemorrhage
2. Oculomotor paresis with cyclic spasm is distinguished from ocular neuromyotonia by its cyclic nature and which of the following:
   a. interval between radiation and onset of symptoms
   b. 3rd nerve weakness between spasms
   c. pupillary involvement
   d. unilateral vs bilateral involvement
3. Which of the following has been considered to play a role in the pathogenesis of ocular neuromyotonia:
   a. segmental demyelination and remyelination
   b. central reorganization involving brainstem nuclei
   c. ephaptic transmission
   d. accumulation of extra-cellular potassium
   e. all of the above

INTRODUCTION
Radiation treatment (RT) can result in a spectrum of injury to central and peripheral nervous system structures. In some respects, an increased understanding of the risk factors for such injury and continued developments in more accurate delivery of treatment have helped to limit complications. On the other hand, the incidence of radiation-related nervous system injury may increase as conventional techniques are applied more aggressively, new approaches are becoming more commonplace and patients are surviving longer.

Variables that influence toxicity (see Table 1)
A number of factors influence the occurrence of radiation damage. These can be divided into 1) treatment factors, 2) host factors, and 3) factors related to the tumor.
1. Treatment factors that affect the incidence of neurotoxicity include: the total dose, dose per fraction, duration of treatment and volume of tissue treated. In general, the incidence increases and latency decreases with larger total doses, higher fraction size and larger volumes of tissue treated.
   - Toxicity is also influenced by the type of radiation employed. Conventional radiation treatment, also referred to as external beam radiation, is traditionally delivered in once daily fractions. More recently, such treatment is sometimes given 2 or more times per day, termed “hyperfractionated”. Shorter, more intense dosing can be delivered via stereotactic radiosurgery (by gamma knife or linear accelerator). In other cases, RT can be delivered intra-operatively or by interstitial implantation, termed “brachytherapy”.
2. Host factors include: age, presence of vascular disease, concurrent chemotherapy, other neurologic disease, and genetic disorders that predispose to tumors.
3. Disease factors: proximity of the target tumor to nervous system structures, surrounding edema, and tumors compatible with longer survival.

In addition to the above variables, the intrinsic radiation sensitivity of different neural structures varies (retina > optic nerves > brainstem, cranial nerves).

TABLE 1: Factors predisposing to radiation-induced neurologic injury

<table>
<thead>
<tr>
<th>Treatment factors</th>
<th>Disease factors</th>
<th>Patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High total dose (&gt;5000 cGy)</td>
<td>Close proximity of target to nervous system structures</td>
<td></td>
</tr>
<tr>
<td>Large fraction size (&gt;200 cGy)</td>
<td>Large amount of peri-tumoral edema</td>
<td>Young age (&lt;12 years, especially &lt; 5 yrs)</td>
</tr>
<tr>
<td>Volume of tissue treated</td>
<td>Tumors compatible with long survival</td>
<td>Old age (&gt;60 yrs)</td>
</tr>
<tr>
<td>Novel delivery technique (stereotactic; brachytherapy; accelerated hyperfractioned)</td>
<td>Vascular risk factors (hypertension, diabetes, hyperlipidemia)</td>
<td>Concurrent chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetic predisposition (eg neurofibromatosis, retinoblastoma)</td>
</tr>
</tbody>
</table>
Forms of neurotoxicity (see Table 2)
Clinical patterns of neurologic injury can be grouped based on the time of onset in relation to treatment.

1. Acute encephalopathy occurs during treatment, often within 24 hours.
   The mechanism involves disruption of the blood brain barrier, leading to edema which may cause increased intracranial pressure. Release of excitotoxic neurotransmitters may also play a role. Manifestations usually include headache, nausea, and worsening of previous deficits. Symptoms can be treated (and largely prevented) with corticosteroids. This complication has become less common due to the routine use of steroids during radiation treatment.

2. Early delayed encephalopathy typically occurs 2 – 4 months after treatment and is due to demyelination caused by oligodendrocyte dysfunction. Manifestations may be diffuse or focal. When the brainstem is involved, ataxia, diplopia, nystagmus and dysarthria are characteristic. Neuroimaging findings are consistent with demyelination; hypometabolism on PET scan helps distinguish this from tumor recurrence. Neurologic deficits are usually reversible with steroids and do not recur, although occasional cases with poor outcome are reported.

   An example of this form of encephalopathy involving ocular motor function was reported by Rider et al. This patient developed 6th nerve weakness one month after RT for recurrent basal cell carcinoma of the ear. Postmortem examination showed extensive brainstem demyelination. In another example, a patient developed transient bilateral internuclear ophthalmoplegia and ptosis after RT, chemotherapy and intrathecal MTX for mediastinal T-cell lymphoma. Eventual post-mortem examination showed no pathologic changes. Transient elevation of myelin basic protein in this case supported the concept of demyelination as the cause.

3. Late delayed encephalopathy is a more common and more serious complication of RT. The mechanism is more complex and not fully elucidated. The three main hypotheses involve: 1) direct damage to glial cells, 2) endothelial damage, and 3) immune response causing a hypersensitivity reaction. There is less evidence for the latter mechanism. Other possible mechanisms involve disruption of cellular DNA, changes in apoptosis, depletion of oligodendroglial and neural stem cell populations, and alterations in cytokine expression.

   Late delayed encephalopathy may take the form of diffuse or focal brain injury. Diffuse injury usually occurs about 1 year after treatment (even as early as 2 – 3 months) and is manifest as cognitive decline, gait impairment, visual–spatial and fine motor deficits. Changes on MRI predominantly affect white matter.

Focal forms of radiation necrosis have variable presentations, including dysfunction of optic nerves/chiasm and less commonly ocular motor nerves (see below). Onset is usually 1 to 2 years after treatment (range 3 months – 19 years). The overall incidence is 3 – 5% in patients receiving doses >5000 cGy. Delayed radiation necrosis occurs with conventional, proton-beam, stereotactic and brachytherapy with a higher (approx 20%) incidence after stereotactic RT.

The usual differential diagnosis is recurrent tumor. MR in radiation necrosis (RN) shows increased T2 signal with variable enhancement, particularly in the peri-ventricular area. Standard MR sequences are not necessarily helpful for distinguishing RN from recurrent tumor; other modalities are more helpful. Single photon — emission computed tomography (SPECT) scanning shows decreased uptake; functional MR shows decreased perfusion. PET scanning typically showing decreased metabolic activity in RN whereas activity is increased in recurrent tumor. PET scanning provides the most specificity, however in some cases biopsy is still needed to make this distinction.

<table>
<thead>
<tr>
<th>Time Course</th>
<th>Onset during treatment</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td>edema ? release of excitotoxic neurotransmitters</td>
</tr>
<tr>
<td>Subacute</td>
<td>1 to 6 months post RT</td>
<td>demyelination</td>
</tr>
<tr>
<td>Late</td>
<td>&gt; 6 months average ~ 14 months</td>
<td>neurovascular damage disruption of cellular DNA ? increased apoptosis ? other</td>
</tr>
</tbody>
</table>

Cerebrovascular changes
RT may produce changes in large vessels, usually due to accelerated atherosclerosis, occurring from 4 months to >20 years after treatment. Such secondary vascular changes occur more frequently in patients with other vascular risk factors and in children, those with NF1, and in patients also receiving concomitant chemotherapy. A Moyamoya pattern affecting the circle of Willis, in which large vessel occlusion is accompanied by multiple small collateral vessels, is sometimes seen, particularly after radiation of chiasmal gliomas in children. In patients surviving 5 yrs or more after cervical RT, hemodynamically significant carotid disease (17% by ultrasound), symptomatic carotid disease (12%) and stroke (6.9%) are common. Clinical sequelae of RT–induced vascular disease are similar to those of standard atherosclerosis, including TIA’s and stroke.

In addition to vaso–occlusion, RT may produce intracranial hemorrhage, presumably secondary to telangiectasias or aneurysm, usually years after treatment. Aneurysms
Cranial (Ocular Motor) Nerve Palsy

Injury to cranial nerves is considered a form of late onset radionecrosis. Onset ranges from 1 to 37 years after treatment with a mean of 5.5 years. In a review from Taiwan of 1032 patients receiving external beam RT for nasopharyngeal carcinoma, 1% developed cranial nerve palsy. Any cranial nerve (CN) can be affected but the nerves differ in their sensitivity to radiation damage. In general, the ocular motor nerves are relatively resistant to damage from RT. One study reported the findings in a group of 25 patients with who developed CN palsy after RT for head/neck tumors. This group had a total of 35 CN palsies, including the 12th nerve in 19 cases, the 10th nerve in 9, 11th nerve in 5, and 5th and optic nerves in one case each. In a group of 19 patients with radiation-related CN palsy who were treated with external beam radiation for nasopharyngeal carcinoma, none involved the ocular motor nerves.

CN damage can also occur with proton beam RT. In an early report, 3 patients developed ocular motor nerve palsies 10–24 months after proton beam RT for pituitary adenomas. All 3 of these patients had been previously treated with conventional RT. Urie et al reported the results of fractionated proton beam RT for skull base tumors in a total of 27 patients. There was CN injury involving 17 nerves in 5 patients. Only 3 of these cases involved ocular motor injury. Using pooled data with logistical regression, these authors reported 1% CN injury at 60 CGE and 5% at 70 CGE. For these calculations, all nerves were pooled together, including optic nerves.

A number of reports have documented the results of stereotactic RT for pituitary and other skull base tumors including the effects on ocular motor nerves. Tishler et al reported the findings in 62 patients treated with radiosurgery for tumors in or near the cavernous sinus with a median follow-up of 19 months. New CN palsy (not involving the afferent visual pathways) occurred in 8 patients (13%), only 3 of which involved the ocular motor nerves. Doses ranged from 1000 to 4000 cGy with an interval following treatment of 2 to 28 months (median 10 months). Most palsies were not severe and only 5 (8%) were permanent. Roche reported no new ocular motor deficits in 80 patients with cavernous sinus meningiomas treated with gamma knife. In this series, of 54 patients with preceding ocular motor deficits, 15 improved, 8 recovered and one worsened (1.3%). In contrast, 21 of 44 patients with eye movement disorders showed improvement following treatment.

**TABLE 3: Radiation induced intracranial neoplasms**

<table>
<thead>
<tr>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma (most common)</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Glioma</td>
</tr>
<tr>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
</tr>
<tr>
<td>Fibromyxosarcoma</td>
</tr>
<tr>
<td>Ependymoma</td>
</tr>
<tr>
<td>Schwannoma</td>
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Leber et al reported the results of gamma knife treatment in 50 patients with middle fossa benign tumors. The 3rd, 4th and 6th nerves were exposed to 5 – 30 Gy or more with no cases of new CN palsy. Morita reported on a similar series consisting of 88 skull base meningiomas treated with radiosurgery among whom there was one 3rd and one 4th nerve palsy, occurring at 7 and 8 month follow-up. In the report of Stafford et al, of 190 patients with skull based meningioma treated with gamma knife, 15 (8%) developed CN palsies including 2 patients with 3rd NP and 3 with 6th NP. Median onset after treatment was 6 months (range 1 – 98 months).

Pollock et al reported 49 patients treated with cavernous sinus meningioma treated at the Mayo Clinic with stereotactic radiosurgery as primary modality (ie, not repeat RT). For example, in one series of patients treated with stereotactic radiosurgery, 25% of previously irradiated patients developed ocular motor palsies. In another report, diplopia occurred in 4 of 9 patients after proton beam RT for acromegaly. In some of these cases diplopia is transient, suggesting a possible role of demyelination.

The risk of radiation induced CN palsy increases after repeat RT. For example, in one series of patients treated with stereotactic radiosurgery, 25% of previously irradiated patients developed ocular motor palsy vs 11% of untreated pts. In a series of 128 acromegalics, 37 developed ocular motor palsies following proton beam RT. In this group of 37 patients, CN palsy developed in 31% of those who had received prior conventional RT vs 14% of those without such treatment.

Abnormal muscle relaxation
Ocular neuromyotonia
This uncommon disorder is characterized by paroxysmal ocular misalignment due to spontaneous repetitive firing of an ocular motor nerve, usually occurring after radiation treatment of a sellar or para-sellar tumor. The first description of ocular neuromyotonia was probably by Johns et al in 1962 but the case was complicated by myasthenia and thyroid orbitopathy. First description of the disorder is usually attributed to Clark (1966) but the term ocular neuromyotonia was first used by Ricker and Mertens in 1970. Since then a number of individual cases and small series have been reported.

Twenty-nine (54%) of 54 reported cases of ocular neuromyotonia (ONM) have occurred after radiation treatment, including a wide variety of tumors (pituitary adenoma, craniopharyngioma, thalamic glioma, chondrosarcoma, chordoma, rhabdomyosarcoma, ethmoid carcinoma, medulloblastoma and ependymoma). The interval between radiation and onset of abnormal eye movements ranges from 2 months to 30 years with a mean of 2.6 years. Age at onset has ranged from 6 years – 74 years. The total RT dose ranges from 20 to 77 Gy (mean 5100 cGy). Most reported cases have followed external beam RT but ONM has also been described after stereotactic RT. In the 3 cases reported by Much et al, ONM occurred at 1 year, 3 yrs and 5 yrs after gamma knife treatment. In one unusual case ONM was due to very low–grade radiation emitted by thorium dioxide (Thorotrast) given for myelography 30 years previously. Cases unrelated to RT have also been reported.

Abnormal eye movements in ONM are due to abnormal extra–ocular muscle contraction rather than weakness. These involuntary contractions are usually induced by eccentric gaze but may also occur spontaneously. Spasms were evoked by eccentric gaze in 17/24 patients in whom this observation was documented. Episodes occurred spontaneously 15 of 18 patients. Abnormal contraction persists for seconds to minutes, including after return to primary position. Sustained contraction is usually followed by a refractory period.

ONM usually affects previously normal nerves. Even after the development of abnormal contractions, baseline ocular motor function is usually normal. Of 54 reported cases, the 3rd nerve was affected in 30 (55%), 4th nerve in 4 (7%) and 6th nerve in 20 (37%). In most cases a single nerve is involved but rare cases have been described affecting multiple nerves. A case with ipsilateral 3rd and 6th nerves was reported by Yee and Purvin and one with bilateral 3rd nerve ONM was reported by Morrow et al.

Damage to ocular motors nerves in ONM is usually in the vicinity of the cavernous sinus portion of the nerve. Histopathologic studies indicate segmental demyelination, axonal degeneration, axonal sprouting and remyelination. Pathogenesis involves delayed muscle relaxation caused by repetitive firing in peripheral nerves triggered by a neural impulse. This delayed relaxation is presumably
related to spontaneous discharge of unstable axons transmitted to adjacent neurons by ephaptic transmission. These axons may be unstable due to previous demyelination followed by remyelination. It has been suggested that accumulation of extracellular potassium, demonstrated in other forms of peripheral nerve hyperexcitability, may play a role as well. Other possible mechanisms involve central reorganization in brainstem nuclei secondary to retrograde degeneration, ephaptic transmission in brainstem nuclei and reorganization of patterns of motor output in ocular motor nuclei.

ONM has not been documented as a sign of recurrent tumor. In most cases the clinical findings are sufficiently characteristic that extensive work-up for recurrent tumor or other etiologies is not needed. ONM usually responds dramatically to carbamazepine which provides lasting relief from symptoms. Gabapentin has also been reported to be beneficial. Cases with spontaneous resolution have been documented. The differential diagnosis of ONM includes 3rd NP with aberrant regeneration, ocular motor paresis with cyclic spasm (see below), superior oblique myokymia, convergence spasm and myasthenia.

Oculomotor paresis with cyclic spams

Oculomotor paresis with cyclic spasm is characterized by an underlying 3rd nerve palsy with superimposed episodes of 3rd nerve overaction. This rare disorder is usually congenital but acquired cases have been also reported. Miller and Lee reported two cases that occurred after radiation of a skull base tumor. These patients developed unilateral 3rd nerve weakness with episodes of spasm 2 and 13 years after radiation. Duration of the cycles was 2–3 minutes in one case and 3–4 in the other. These patients differed from those with typical ONM in that their motility was abnormal between spasms (in contrast to most cases of ONM) and because their normal EOM contraction was cyclic rather than induced by eye movement or random (non-rhythmic). The authors cited 5 previously reported cases of ONM with cycles of spasm and some degree of 3rd nerve weakness. In contrast to the cases of Miller and Lee, these previous cases had only minimal evidence of underlying 3rd nerve paresis and none exhibited continuous, predictable cycles. Furthermore, spasms could not be induced by eccentric gaze in the cases of Miller and Lee and treatment with carbamazepine (in one patient) was unsuccessful.

The authors point out that the mechanism in their cases of oculomotor spasm with cyclic spasm (COPS) is likely similar to that of ONM. Previous theories of pathogenesis in COPS implicate partial damage to the intracranial oculomotor nerve, followed by retrograde degeneration producing secondary changes in the nucleus. This theory postulates two surviving populations of neurons, those that are injured (paretic) and those that are hyperactive. This model is similar to theories regarding mechanism in OMN (as above).

Ocular neuromyotonia with 3rd nerve synkinesis

Several cases of ONM in conjunction with oculomotor synkinesis have been reported. This combination of findings lends further support for the concept that the findings in ONM are related to damage and subsequent regeneration of the ocular motor nerve. Rather than considering this a rare occurrence, Plant has stated that most of the patients he has seen with ONM have shown some sign of synkinesis as well. This synkinesis has reportedly improved with carbamazepine in two cases and both may regress spontaneously in parallel.

Miscellaneous variants

Other rare variants and associations of ONM have been reported. A case affecting the 5th nerve rather than an ocular motor nerve has been reported and also a case associated with Adie’s pupil. Oohia et al described a case of ONM accompanied by spastic lid closure as well as 3rd nerve synkinesis. The basis for this apparent 7th nerve involvement is unclear and it has been suggested that intermittent eye closure might have been a means of preventing diplopia.

Diagnosis of radiation neuro-ophthalmic toxicity

Diagnosis is based, in large part, on the timing of the neurologic syndrome. Symptoms that occur during treatment are likely related to edema and typically respond to steroid treatment. Sixth nerve palsy may occur in this setting secondary to increased ICP. Double vision, gaze palsy or nystagmus that occurs within 2 months of radiation is most likely due to brainstem demyelination. Damage should be visible on FLAIR and T2-weighted MRI and usually responds to steroid treatment. Appearance of a new symptom or lesion within 8 months of conventional RT often indicates tumor recurrence. Diplopia that occurs about 2 years after treatment may be due to delayed radiation necrosis involving cranial nerves however this is an unusual occurrence and therefore strong consideration should be given to the possibility of recurrent tumor. Skull base tumor is often challenging to demonstrate with neuroimaging, particularly in the presence of post–operative changes. Intermittent diplopia occurring some years after RT should suggest the possibility of abnormal EOM relaxation. While this most often takes the form of neuromyotonia, other related phenomena such as oculomotor palsy with cyclic spasm or aberrant regeneration also occur. Ocular motor deficits occurring many years after radiation treatment may be due to a second neoplasm or to stroke secondary to vaso–occlusive disease.

CME ANSWERS

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REFERENCES


