Instructions:

• Each speaker will prepare a syllabus that must be submitted through the online submission system.
• The length of the syllabus will be no shorter than 4 single spaced pages in essay (not point) format, plus references.
• Use single spaced, 11 point type and (if possible) Times New Roman font.
• When typing the text use word wrap, not hard returns to determine your lines.
• If headings and subheadings are used, these may be highlighted by using all caps and bold.
• Do not use the header or footer feature or endnotes in preparing the text.
• The submission must be submitted online.

Title:

Diagnosis and Treatment of Paraneoplastic Syndromes

Learning Objectives:

1. Describe the spectrum of paraneoplastic syndromes with neuro-ophthalmic features
2. Define the challenges in diagnosis of the paraneoplastic syndromes
3. Explain the therapeutic options for treatment of these diseases

CME Questions:

1. The presence of serum antibodies against recoverin
   a. are pathognomonic for CAR
   b. are found in the majority of patients with lung cancer
   c. may be responsible apoptotic cell death in CAR patients
   d. are best detected by immunofluorescent studies on retina

2. Which of the following is correct regarding therapy for paraneoplastic neuro-ophthalmic disease:
   a. steroid therapy may be helpful in control of disease
   b. should be initiated only after there is validation for the presence of autoreactive antibodies
   c. cytoreduction of the primary tumor is not helpful in controlling the autoimmune component
   d. biologic immunomodulatory agents have no role in therapy

3. Lambert-Eaton myasthenic syndrome is associated with which of the following:
   a. symptoms and signs that are indistinguishable from myasthenia gravis
   b. antibodies against the acetylcholine receptor
   c. absence of autonomic symptoms in the majority of patients
   d. clinical response to 3,4-diaminopyridine

Keywords (Max 5):

1. paraneoplastic
2. cancer associated retinopathy
3. melanoma associated retinopathy
4. Lambert Eaton syndrome
5. opsoclonus/myoclonus

Introduction/Abstract (Please see instructions for formatting details):
Neuro-ophthalmic consequences of paraneoplasia may involve multiple aspects of the afferent visual pathway from the uvea to the optic nerve and the efferent pathways for eye movement.\(^1\)\(^6\) It is important to understand the spectrum of signs and symptoms that can result from a tumor-stimulated immune process in order to both suspect, diagnose and treat these diseases.

**Body (Please see instructions for formatting details):**

**CLINICAL DISEASE SPECTRUM**

When should the astute clinician consider a diagnosis of paraneoplastic syndrome? In terms of afferent symptoms, an unexplained, painless, progressive vision loss is typical. In the retinal diseases, there may be photopsias, night blindness, or ring scotomas. In the optic neuropathies there is most commonly bilateral disc swelling often accompanied by a vitritis. Efferent symptoms include myasthenic-like presentation or the presence of opsoclonus-myoclonus. Associated systemic neurologic symptoms, such as encephalitis, cerebellar degeneration, myelitis, or sensory neuropathies, increase suspicion for a paraneoplastic syndrome. Pertinent negatives include lack of alternative explanation for the symptoms such as a known genetic condition, history of ocular surgery, infection, trauma, mass lesion, or toxic exposures. A history of cancer may heighten the suspicion for a paraneoplastic syndrome, but the real challenge is to help diagnose a potentially treatable cancer in patients who do not already carry that diagnosis.

**Afferent symptoms**

**Autoimmune paraneoplastic retinopathy.** Three types of syndromes of autoimmune paraneoplastic retinopathy have been described in the literature: cancer associated retinopathy (CAR), melanoma associated retinopathy (MAR) and, bilateral diffuse uveal melanocytic proliferation (BDUMP).\(^7\)\(^14\) CAR was the first of these syndromes to be recognized, appears to be the most common of the paraneoplastic retinopathies, and remains a significant diagnostic and therapeutic challenge.\(^7\)

Visual dysfunction in CAR typically involves a bilateral, progressive and painless loss of vision with photopsias.\(^9\)\(^15\) Patients complain of a rapid onset of night blindness and flickering lights associated with progressive vision loss over weeks to months. However, the signs and symptoms depend on whether rod or cone function is primarily disrupted. In rod disease, there is often constriction of the visual field with impaired dark adaptation. In contrast, when there is primarily cone dysfunction, central scotomas, dyschromatopsia, and loss of visual acuity are more prominent. There may be an associated uveitis. Retinal findings may be unexceptional, alternatively arteriolar narrowing, thinning or mottling of the retinal pigment epithelium (RPE), or pallor of the optic disc may be observed in these patients. Electroretinography (ERG) confirms photoreceptor dysfunction but is not pathognomonic for CAR. CAR may occur in patients with known malignancies, however it may also occur before the diagnosis of cancer, and thus prompt recognition of this disease may lead to early diagnosis and cure for patients with specific types of malignancies. Although the most common tumor associated with CAR is small cell lung carcinoma, other tumors originating in many organs including the prostate, bladder, colon, thymus, ovary, endometrium, breast, and cervix have also been implicated in CAR (Table 1).

Visual symptoms in MAR have a rapid onset and include loss of visual acuity, presence of photopsias, and central or paracentral scotomas.\(^6\)\(^7\)\(^17\) The vision loss is usually mild with acuities generally in the 20/60 range. Ophthalmoscopy may be initially normal but ERG abnormalities are present, including reduced scotopic a-wave and decreased or absent dark-adapted b-wave. In a large review of more than 60 patients with MAR, vitreous cells were present in 30% of affected patients.\(^17\) However, the fundus evaluation was initially normal in more than 40%. Similar to CAR, disc pallor and retinal vascular attenuation may be observed. Patients with MAR usually have a diagnosis of malignant melanoma that predates the retinal disease by several years.

BDUMP is rare but distinctive in its proliferation of melanocytes in the uveal tract along with bilateral loss of vision. These patients are present with sudden and bilateral visual loss and may have exudative retinal detachment and progressive cataracts. This entity is rare and the patients reported typically had a short life span, less than 15 months following diagnosis on average. Visual disturbance may precede diagnosis of malignancy, and although multiple types of cancers have been identified in association with BDUMP, the most common are lung or gynecologic in origin.

**Paraneoplastic optic neuropathy.** Paraneoplastic optic neuropathy (PON) is an unusual but serious cause of bilateral, painless loss of vision. In 2003 a cohort of 16 patients were identified as being positive for the antibody against CRMP-5.\(^18\) More than 90% of these patients, in concordance with others reported since then in the literature, have a prominent
complaint of vision loss, which is painless and either acute or subacute. Similar to patients with CAR and MAR, photopsias may be present. Ophthalmoscopic findings in these patients classically include optic disc edema and vitreous cells, but patients may present with optic atrophy as well. Retinitis may also be present, and ERG in these patients may show abnormalities in scotopic rod, scotopic combined rod-cone, or photopic cone response. Vitreous cells appear small, without clumping, and without evidence for an intermediate uveitis. Evaluation of vitreous cells reveals pleomorphic lymphocytes. One of the original 16 patients described also had anterior chamber cells, an unusual finding in this disease. In addition, disorders of eye movement including vertical gaze disturbance, internuclear ophthalmoplegia, and opsoclonus have been observed in affected patients. Systemic neurologic symptoms are present in essentially all of the patients during their illness and may include seizures, dementia, cognitive abnormalities, cerebellar findings and a wide variety of motor and sensory abnormalities. Concomitant Lambert-Eaton syndrome has also been described in association with PON. The most common associated cancer in these patients is small cell lung carcinoma. Less common associations include other lung cancers, renal cell carcinoma, colon cancer, papillary thyroid cancer, breast, uterine, and neuroendocrine tumors.

**Efferent symptoms**

**Opsoclonus/myoclonus syndrome.** Myoclonus is defined by short, sudden involuntary jerking movements which may involve lower or upper extremities and may be induced or worsened by a change in posture. Opsoclonus is the ocular concomitant of myoclonus, and is characterized by rapid, involuntary, horizontal and vertical eye movements without intersaccadic delays. In children, up to 43% of cases of the opsonolus-myoclonus syndrome (OMS) were associated with a paraneoplastic syndrome associated with neuroblastoma. In 2011 a series of adults with OMS was described in conjunction with a review of all reported cases of adult OMS. In this series the age range for the newly reported patients was 27-78 years and symptoms consisted of dizziness/balance difficulties in 67%, nausea/vomiting in 48%, and abnormalities of vision from opsonolus in 28% of patients. Neuroimaging was normal in all except one patient with metastatic disease. Evaluation of CSF revealed abnormalities in more than 50% including elevated protein and/or increased white cells (lymphocytes) in the majority; in about a third of cases there may be an increased IgG index or oligoclonal bands. Etiologies for OMS included cancer in 15% (breast adenocarcinoma and small cell lung cancer) and parainfectious in the remaining patients; notably in the review of the literature lung cancer was responsible for 28% of cases and breast cancer for 6% of cases. Other non-malignant causes of OMS in adults are less common and include toxic/metabolic or other autoimmune etiologies.

**Lambert-Eaton myasthenic syndrome.** In the Lambert-Eaton myasthenic syndrome (LEMS) there is a decrease in acetylcholine release leading to decreased activity of the neuromuscular junction. Although LEMS is typically characterized by decreased deep tendon reflexes, autonomic dysfunction, and proximal muscle weakness, symptoms of diplopia and ptosis may be common. In fact, the autonomic symptoms develop in about 90% of affected patients within the first three months of disease onset and are very helpful in identifying the diagnosis as LEMS. To distinguish LEMS from myasthenia gravis (MG), clinical findings, such as slight increases in strength on prolonged effort, and electromyography, showing facilitation in repetitive stimulation testing, when present may help make the diagnosis. Ocular symptoms generally occur after onset of other disease symptoms such as generalized weakness and ultimately occur in about half of patients with LEMS. Ocular findings reported in patients with LEMS, that are not generally seen in MG include involuntary lid closure, decreased ptosis with prolonged upgaze, dilated pupils, and poorly reactive pupils. Ductions are typically full in LEMS, but may be limited in MG. More than 50% of patients with LEMS have cancer, commonly lung cancer, but also lymphoproliferative diseases as well as cancers of the prostate or thymus have been disease associated.

**PATHOPHYSIOLOGY**

The paraneoplastic syndromes discussed in this session involve antibodies against normal proteins that are also typically expressed in the tumor. To date a virtual alphabet soup of proteins have been identified as potential immune targets and in some cases these proteins have been validated as playing a significant role in the pathophysiology of the disease (Table 1). For other candidates, the pathophysiological role played by the immune response against a particular autoantigen is not entirely clear.

Recoverin, a 23 kDa protein, is one of the first antigenic targets identified that is associated with CAR. The protein is widely expressed in the majority of lung cancer samples, irrespective of retinopathy. Serum autoantibodies against recoverin may be present in small subset of patients with lung cancer, but only a small fraction of those develop CAR. Alpha-enolase, another common protein that is found both in lung cancer and the retina elicits an antibody in a larger percentage of patients with lung cancer (estimated at 13-65%); however only a small subset of these patients will develop CAR. Alpha-enolase antibodies are also found in many other diseases, including autoimmune hepatitis, rheumatoid arthritis, and mixed cryoglobulinemia, but also can be found in normal individuals as well, thus the presence of the antibody alone does not indicate disease or causation of symptoms.
Therefore, how are these antibodies associated with disease pathophysiology? It is believed that high-titer antibodies may traverse the blood-retinal barrier, leading to exposure to retinal cells. There is also some evidence for different antigenic epitopes within a protein with differential consequences with regards to pathology. In addition, the immunologic phenomenon of epitope spreading is postulated to be associated with differences in pathogenic sequelae. In the retina there is some evidence that the antibody may be engulfed through an endocytic mechanism into retinal cells. Once internalized, the antibody engages its corresponding antigen and this binding leads to downstream signalling resulting in apoptotic cell death. This observation was initially made in vitro using retinal cells in culture, but has also been replicated in vivo using either intravitreal or intravenous injections of antibodies against recoverin. Apoptosis was activated through caspase 3 and caspase 9. It is believed that an increase in free Ca$^{2+}$ precedes apoptosis, a mechanism that was also observed in studies using antibodies against enolase. In studies using anti-enolase antibodies there is a decrease in glycolytic adenosine triphosphate with resultant increase in the intracellular Ca$^{2+}$. Therefore, this mechanism is a plausible common pathway leading to cell death. However additional studies will be required to definitively understand the disease pathophysiology. Many other potential antigens have also been identified but it is yet unknown whether the antibodies against these antigens play an important role in disease pathogenesis.

In LEMS there is a well-characterized antibody against P/Q voltage-gated calcium channels (VGCC), present on the presynaptic nerve terminal at the neuromuscular junction. This antibody reproduced the disease in in vivo animal models and the disease can be transmitted passively from mother to child. It is believed that the antibody causes a loss in the VGCC, leading to a decrease in Ca$^{2+}$ internalization and subsequent decrease in release of acetylcholine containing vesicles, thus there is less available acetylcholine at the neuromuscular junction.

**LABORATORY EVALUATION**

For the well-characterized antigens in disease pathophysiology, such as CRMP-5 and recoverin, the presence of antibodies is helpful in making the diagnosis. The challenges are primarily: 1) interpreting and identifying possible disease-associated antibodies against other possible antigens, and 2) understanding the sensitivity and specificity for the known antigens in helping to make the diagnosis of a paraneoplastic condition. Laboratory evaluations for the presence of antibodies are performed using multiple techniques. In immunofluorescence testing, a section of tissue is exposed to sera from the patient and then the bound antibodies are visualized using a fluorescently tagged second antibody that globally recognizes the type of bound antibody, for example IgG. Immunofluorescence testing simply identifies whether or not the serum binds to a tissue, but does not identify the antigens. Particular patterns of binding, types of cells or subcellular preferences (nuclear, cytoplasmic, perinuclear) may be helpful in identifying a likely type of antibody. In immunofluorescence testing the origin and type of tissue, fixation protocol, and incubation time with the serum, and serum dilution are all critical in obtaining an interpretable result. In Western blot testing, a mixture of proteins, generally obtained from cell culture or tissue homogenization are separated on a gel using an electric current, transferred to a nitrocellulose membrane, exposed to the serum, and the bound antibody is identified using a tagged second antibody that allows for visualization. Here the pitfalls are many and include the tissue or cells of origin, the way that the proteins are extracted from the tissue or cells, the dilution and exposure time to the serum, blocking of the membrane to enhance specificity, and the size of the antigen which determines whether it is bound or transferred adequately from the gel to the membrane. In Western blot one identifies the size of the protein, which may be suggestive but is not confirmatory for the identity of the antigen. ELISA testing typically will use a purified protein as the target for antibody detection and therefore provides the greatest specificity when identifying an antibody. The protein is immobilized, exposed to the serum at multiple dilutions, and a tagged secondary antibody is used for visualization. As in the other types of antibody testing, the technique is important. In all of these tests, it is important to understand the limitations of the testing strategy and the false positive and false negative potential for particular evaluations.

Antibodies against self-proteins are fairly common, using Western blot as a criteria the majority of control individuals have immunologic reactivity against at least one protein in whole retinal extracts. A report in 2008 included a review of the literature about antiretinal antibodies and this report suggested that standardization among laboratories was lacking and therefore results were not always concordant between different testing sites. In fact, in a paper published in 2013, serum from 14 patients who were diagnosed as having autoimmune retinopathy was sent to two different laboratories for evaluation of the presence of antiretinal antibodies by Western blot. One laboratory used human retina extract with a positive control and the other used pig retinal extract with a panel of normal controls (without antiretinal activity). They tested serum from all 14 patients and found that antibodies were detected by both laboratories in 64%, of the remaining 5 patients, 4 were positive for antiretinal antibodies as detected by one laboratory and one was positive as detected by the other laboratory. Furthermore, for the 64% that were positive, there was only a single patient whose sera gave the same results (within 1 kDa of size of the band) from both laboratories. Therefore the testing for antiretinal antibodies is not currently standardized and may result in data that is confounding at best.

*What antibodies are known to be disease-associated?* Disease-associated, validated antigenic targets of antibodies have been described in several of the paraneoplastic neuro-ophthalmic syndromes (Table 1). However there are other antigens that have also been identified as potential immunologic targets, but the pathologic significance of these antibodies is
If you suspect CAR then antibodies against retinal proteins are initially tested through Western blot and/or immunofluorescence. As noted above however, it might be important to send materials to different laboratories for investigation. It is likely that over the next several years, there will be standardization of testing, however this is not yet a reality. If the testing is negative, you must consider the possibilities that the patient is negative for antiretinal antibodies or that the technique used was not sufficiently sensitive to uncover the reactivity. In one of the largest series of CAR patients described in the literature, only 61% had antibodies against defined retinal proteins, of which the antigenic targets were alpha-enolase in about half of the patients, followed in descending percentages by transducin, carbonic anhydrase II, and recoverin. In fact, antibodies against recoverin, the best characterized antibody, were found in only 10% of the patients. If the clinical suspicion for CAR remains high, but the antibody testing is negative, then one might try empirical therapy for treatment of CAR, in particular in the setting of known malignancy, to determine if there is improvement in visual symptoms (see management below). What systemic evaluation should be performed for an occult malignancy? Certainly one would obtain a chest CT scan to identify lung or mediastinal lesions. Breast examination and mammography should be performed. Pelvic and abdominal CT would reveal many other cancers that are associated with CAR. Pelvic examination, prostate examination, and colonoscopy should be considered in the appropriate patients. Serologic testing for cancer markers may also have a role in the evaluation. These tests are perhaps best ordered through a collaborative care of the patient with their primary care provider. Whole-body positron emission tomography using fluorodeoxyglucose (FDG-PET) can be performed in patients in whom other testing was not revealing, however FDG-PET will reveal “hot-spots” that are associated with inflammatory and infectious diseases as well as neoplastic disease and therefore the sensitivity may lead to enhanced patient morbidity in terms of additional testing.

If antibody testing is positive, you need to determine whether the results fit the observed clinical picture prior to making the diagnosis. In addition to the high incidence of un-named retinal antibodies mentioned above, antirecoverin antibodies, the best-studied antibody associated with CAR, has also been observed in 1% of patients with retinitis pigmentosa. Therefore the presence of these antibodies is not pathognomonic for CAR.

Patients with MAR most commonly produce antibodies that react with retinal bipolar cells, as visualized by immunofluorescence, however specific antigenic targets are not well-defined although several candidates antigens have been identified. Therefore, MAR is primarily a clinical diagnosis, based on the presenting signs and symptoms, the history of melanoma, and ERG findings that are consistent with the disease. If there is no history of melanoma, but your clinical suspicion is high for MAR, then the patient should be referred for a full dermatologic evaluation and one should consider whether additional testing, such as FDG-PET or other imaging, is prudent.

In the case of PON, antibodies against the CRMP-5 antigen are present and detectable by immunofluorescence studies or Western blot. Patients with the opsoclonus/myoclonus syndrome generally do not have positive paraneoplastic antibody evaluations in the serum or CSF. However, antibodies against ANNA-2, NMDA receptor, nuclear antigens, and neuronal calcium channels have all been seen in subsets of these patients. In fact recent data suggests that antibodies against Purkinje cells may be responsible for disease pathogenesis in some patients. If testing is desired, then serum should be sent for a full paraneoplastic evaluation that will typically use immunofluorescence, for reactivity against brain, and enzyme-linked immunosorbant assay (ELISA), for reactivity against specific antigenic targets as an initial screen followed by additional testing for antigens of high specificity. Given that an antibody is typically not identified, consideration of a paraneoplastic syndrome is pursued by evaluation for occult malignancy.

Specific testing for antibodies against the VGCC should be done in patients who are suspected to have LEMS. These studies are generally available through both academic and community laboratory services as ELISA tests with good specificity. Antibodies against the P/Q-type VGCC are present in 85-90% of patients with LEMS but may also be seen in up to 4% of patients with small cell lung cancer in the absence of neurologic disease. In addition LEMS patients may have antibodies against N-type VGCC (in up to 30-40%) or L-type VGCC (in up to 25%). Occult malignancies in these patients are performed as described for CAR, above. The starting point should be a chest CT, which would reveal the more commonly associated lung or thymus cancer, however male patients will require prostate evaluations, and lymphoproliferative diseases should also be considered in this paraneoplastic condition.

**MANAGEMENT**

A common thread among all of the paraneoplastic syndromes is that treatment of the underlying tumor may be beneficial to the neuro-ophthalmological symptoms and signs. Treatment targeting the antibody mediated paraneoplastic syndrome and symptomatic therapy has also shown some utility.
In addition to cytoreduction of tumor, the mainstay for treatment for CAR is use of oral or intravenous corticosteroids or a combinatorial therapy of cyclosporine, azathioprine, and prednisone with a reported response rate of up to 70%. Newer therapies have included rituximab.34

Many types of therapies have been used with variable success in MAR. Use of local or systemic corticosteroids was generally unsuccessful whereas a single patient received benefit from steroids and several patients received benefit from IVIG, alone or in combination with cytoreduction of tumor burden.17 Successful treatment has been reported with combinatorial therapy such as oral prednisone, plasmapheresis, azathioprine, and gabapentin or the combination of intravenous steroid with plasmapheresis. The total numbers of affected patients are small and therefore best practice is not yet determined for these patients. BDUMP is quite rare but there have been reports of improvement with plasma exchange with or without concomitant corticosteroid.35

Paraneoplastic optic neuropathy in association with CRMP-5 is unusual and is typically also accompanied by a mixed T cell lymphocytic cellular infiltrate at the vitreous and optic nerve.36 Although the usual therapy will include primary tumor treatment as well as systemic corticosteroids, the authors presented two patients in whom disease improvement was tied to the use of intravitreal triamcinolone.

In the opsoclonus-myoclonus syndrome, patients generally respond favorably to treatment with intravenous corticosteroids and/or IVIG.20 In addition to the treatment of the primary tumor with surgery and/or chemotherapy and/or radiation, it is believed that early treatment is associated with a better response to therapy. A wide variety of other agents have been used in small numbers of patients with some success. If long-term corticosteroids are required then steroid-sparing agents could be tried.

Suggested therapy for LEMS includes 3, 4-diaminopyridine, intravenous immunoglobulin (IVIG), plasma exchange, steroids, and immunosuppressive agents.37-40 According to a Cochrane publication that reviewed trials through 2010, there is good evidence for the use of 3,4-diaminopyridine, an agent that increases the release of acetylcholine, and a single trial that demonstrated benefit from IVIG.37 The use of steroid and azathioprine in addition to 3,4-diaminopyridine may be advised, but this is not based on prospective clinical trials.39 In 2013 a new calcium channel agonist, with selectivity for both the N-type and P/Q type VGCC was used in an experimental model of LEMS, with promising results.40 If these results can be replicated in humans then this would give additional therapeutic options.

In conclusion, the paraneoplastic disorders in neuro-ophthalmology may predate identification of a malignancy. These patients require careful discussion about the possibility of an underlying disease such as cancer and also will require periodic follow up. Treatment consists of control of tumor itself followed by symptomatic relief and targeted use of immunomodulatory drugs. The expectation is that new modalities for a standardized diagnosis and targeted therapy will be developed over the next few years.

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<tr>
<th>Syndrome</th>
<th>Defined, Disease Associated Antigen</th>
<th>Autoreactivity Against Specific Cell Type</th>
<th>Suspected, Disease Associated Antigen/Cells</th>
<th>Tumors</th>
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<td>Transducin, Carbonic anhydrase II, Arrestin, TULP1, Neurofilament, HSP-70, TRPM1, Müller-cell-specific Others</td>
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**not otherwise discussed in this report**

**CME Answers (Use lowercase letters if it’s an a/b/c option; feel free to include a description next to the correct answer):**

1. c
2. a
3. d

**References:**


