CE Case Report

Treatment of Cancer-Associated Retinopathy With Rituximab

Irene Dy, MD[a,b]; Rangaswamy Chintapatla, MD[a,b]; Isabel Preeshagul, MD[c]; and Daniel Becker, MD[a,b]

Abstract

Cancer-associated retinopathy (CAR) is a rare autoimmune condition associated with various cancers, causing significant visual impairment. Visual symptoms in CAR may or may not correlate with the extent of systemic disease or its response to chemotherapy, and must be addressed separately from the management of systemic malignancy. Steroids have been the mainstay of CAR therapy. Various immunomodulatory therapies have also been described with varying responses, but the overall visual prognosis remains poor. Rituximab is a monoclonal antibody used in the treatment of non-Hodgkin's B-cell lymphoma and many autoimmune disorders. This case report describes a patient with small cell uterine cancer who initially presented with visual impairment associated with CAR. The patient's deteriorating visual symptoms were successfully halted for an extended, clinically meaningful period with rituximab. (*JNCCN* 2013;11:1320–1324)

NCCN: Continuing Education

Accreditation Statement

This activity has been designated to meet the educational needs of physicians and nurses involved in the management of patients with cancer. There is no fee for this article. No commercial support was received for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians.

NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center`s Commission on Accreditation.

This activity is accredited for 1.0 contact hours. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/31860;** and 4) view/print certificate.

Release date: November 14, 2013; Expiration date: November 14, 2014

Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the etiology, clinical presentation, diagnosis, and management of CAR
- Discuss the rationale for use of rituximab in the treatment of CAR

From the [a]Continuum Cancer Centers of New York; [b]Department of Medicine, St. Luke's–Roosevelt Hospital Center; and [c]Department of Medicine, Beth Israel Medical Center, New York, New York.

Submitted September 23, 2012; accepted for publication April 25, 2013.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Rangaswamy Chintapatla, MD, St. Luke's–Roosevelt Hospital Center, Suite 11G, 1000 10th Avenue, New York, NY 10019. E-mail: rchintap@chpnet.org

Case Summary

A 61-year-old right-handed woman presented in October 2010 with rapidly progressive painless visual dysfunction. She described fluctuating visual changes in the right eye for 4 days and subsequently in the left eye 2 days before presenting to her ophthalmologist. She reported experiencing diminished night vision, flashes of light, and dimming of the visual fields. She denied photosensitivity or headaches. Examination confirmed generalized constriction in her visual fields bilaterally and normal fundi. Electroretinography was flat to scotopia and photopia, and fluorescein angiography revealed window-like defects. She was suspected to have cancer-related autoimmune retinopathy and was referred to an oncologist for further evaluation. She had no detectable antiretinal antibodies.

She was a nonsmoker with no significant past medical history. She denied weight loss, fever, abdominal pain, dysuria, vaginal bleeding, or rash. On further review, she reported a mass in her lower abdomen, which had been causing mild pelvic pressure for approximately 3 days. Physical examination confirmed a non-tender poorly defined suprapubic mass. A CT scan of the chest, abdomen, and pelvis showed paraortic lymphadenopathy at the mediastinal, renal, and retrocrural levels, and an enlarged uterus. She proceeded to diagnostic laparoscopy, which revealed a bleeding uterine mass with hemoperitoneum. She had an emergent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathologic specimens were consistent with a high-grade small cell neuroendocrine cancer of the uterus, with lymphovascular invasion.

Her vision continued to worsen postoperatively and she was started on methylprednisolone, 1 g/d for 3 days, and transitioned to oral prednisone at 1 mg/kg, and experienced subsequent stabilization of visual deterioration. Two weeks after surgery, intravenous carboplatin and etoposide once every 3 weeks was initiated for extensive-stage small cell cancer. After chemotherapy cycle 4, while on 10 mg of prednisone daily, her vision deteriorated acutely despite dramatic reduction of systemic tumor burden. A second course of high-dose methylprednisolone was less effective at stabilizing her vision, and intravenous immunoglobulin (IVIG) was initiated. She received monthly IVIG at 1000 mg/m^2 for 5 doses along with maintenance prednisone, and had stable vision during that time. She completed cycle 5 and 6 of carboplatin/etoposide.

Three months after completion of chemotherapy, her systemic disease progressed, with several new hypermetabolic nodules in the left lower abdomen and posterior mediastinum. At the same time, approximately 8 months after diagnosis and while on 10 mg/d of prednisone, she again experienced narrowing of the visual fields. Her vision stabilized with an increase in prednisone to 60 mg/d. Oral topotecan and rituximab at 375 mg/m^2 weekly for 4 weeks were initiated. Repeat imaging 11 months after diagnosis showed progression of disease and she was started on third-line cyclophosphamide, adriamycin, and vincristine (CAV). Her vision remained stable on tapering dose of prednisone for 4 months after rituximab. A second course of rituximab was initiated for worsening vision 13 months after diagnosis. She progressed through third-line chemotherapy and started paclitaxel 16 months after diagnosis. At that time she was able to drive during the daytime and ski. She died from disease progression 18 months after diagnosis. At the time of her death, she was taking 12 mg/d of prednisone. She had minimal visual deterioration from the initiation of rituximab 8 to 9 months after diagnosis until her death, approximately 9 months later.

Discussion

Paraneoplastic syndromes occur in 10% to 15% of malignancies and are most often associated with carcinomas of the lung, breast, and ovary. Cancer-associated retinopathy (CAR) is a heterogenous group of paraneoplastic autoimmune disorders resulting from immunologic cross-reactivity between the tumor tissue and retina.[1] CAR was first described by Sawyer et al[2] in 1976 in 3 patients with lung cancer. It is most commonly associated with small cell cancers of the lung and gynecologic cancers, but associations with lymphoma and breast, non–small cell lung, prostate, pancreatic, bladder, colon, and larynx cancers have been described.[3] Circulating antibodies cause destruction of cross-reacting antigens expressed by rods, cones, or retinal ganglion cells, leading to visual impairment.[3] Recoverin, a 23-kDA retinal protein, is the most common antigen associated with CAR. Mutations involving the *p53* tumor suppressor gene on chromosome 17 lead to overexpression of recoverin, a highly immunogenic protein that stimulates production of anti-recoverin antibodies.[1]

Recoverin-specific antibodies bind to the antigen in photoreceptor cells and lead to ion channel closure, depolarization of the cells, and, ultimately, photoreceptor cell degeneration.[3]

CAR typically presents with subacute bilateral vision abnormalities progressing over weeks to months, ultimately leading to bilateral vision loss. Patients often complain of flickering or shimmering of lights. CAR can affect cones and/or rods bilaterally. Cone dysfunction causes photosensitivity, decreased visual acuity, decreased color vision, and central scotomas, whereas rod dysfunction causes nyctalopia, prolonged dark adaptation, mid-peripheral scotomas, and peripheral field deficits.[1] Jacobson et al[4] proposed the triad of photosensitivity, ring scotoma, and attenuated retinal arteriole caliber to be associated with CAR. Early in the disease, funduscopy may be normal and disease progression leads to attenuation of the arterioles and mottling of the retinal pigment epithelium. Electroretinography frequently identifies irregularity associated with CAR. Patients with primarily rod dysfunction are characterized by abnormal scotopic electroretinography, whereas those with cone dysfunction are characterized by abnormal photopic electroretinography.[1] Serum antiretinal antibodies can be detected by Western blot, enzyme-linked immunosorbent assay, or immunohistochemical methods.[1]

Review of the literature revealed no specific correlation between the response of the underlying cancer to therapy and visual abnormalities. Eltabbakh et al[5] reported on a 65-year-old woman with uterine sarcoma whose CAR resolved after surgical debulking and chemotherapy. Sekiguchi et al,[6] however, reported on a 60-year-old woman with stage IB small cell carcinoma of the uterus who completed surgical debulking without any visual improvement, but experienced some improvement in vision with steroid therapy. Glucocorticoids may transiently halt visual deterioration in some patients.[3] No specific guidelines are available for the management of this rare disease, but most authors used methylprednisolone up to 1 g/d, followed by taper to 60 to 100 mg of oral prednisone daily.[3] Other forms of immune-modulator therapies, such as IVIG,[7] plasmapharesis,[5] Tolpa Torf Preparation,[8] cyclosporine, and alemtuzumab,[9] have been used with some success.

Rituximab is a monoclonal antibody against CD20 primarily used in the treatment of non-Hodgkin's B-cell lymphoma. CD20 is a cell surface antigen specific to B cells, and is present on all B cells except plasma cells. Rituximab is used in the management of a wide variety of autoimmune diseases, such as rheumatoid arthritis, immune thrombocytopenia, lupus, autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, graft-versus-host disease, multiple sclerosis, and neuromyelitis optica.[10] Putative mechanisms of action of rituximab include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, apoptosis, and increased phagocytic activity of the reticuloendothelial system.[10,11] The "decoy hypothesis," further proposes that rituximab-IgG molecules bind to circulating effector cells, such as neutrophils, monocytes, and macrophages, reducing the availability of effector cells at the site of immune complex deposition and slowing tissue damage.[11] The authors chose rituximab given its success in treating autoimmune disorders.

This report presents an uncommon case of a patient with small cell carcinoma of the uterus with CAR in whom visual deterioration was successfully halted by the use of rituximab. In this patient, visual symptoms did not correlate with the systemic disease activity or disease response to cytotoxic chemotherapy, but seemed to stabilize with rituximab therapy. She had no detectable antiretinal antibodies, and response to therapy was monitored clinically. To the authors' knowledge, only one previous report of rituximab use in CAR has been published.[12] Visual symptoms of CAR preceding the diagnosis of uterine cancer are also rare, and only 5 similar cases have been reported (Table 1).[6,8,13–15] The cases were predominantly in postmenopausal women, with a median age of 63.4 years, who presented at an advanced stage. The median survival was less than 1 year, and patients experienced transient improvements in vision.

Conclusions

Paraneoplastic syndromes such as CAR can occasionally precede the diagnosis of an underlying malignancy. CAR should be considered in patients presenting with subacute bilateral visual dysfunction of unknown cause. Visual impairment causes severe functional morbidity that must be addressed separately from the management of the underlying malignancy. The patient in this report experienced 9 months of preserved vision after rituximab was initiated, until she died as a result of systemic disease.

Table 1 Reported Cases of Paraneoplastic Retinopathy Associated With Small Cell Cancer of the Endometrium

Study	Age (y)	Stage Visual	Symptoms	Interval Between PR and CA	Antibody to Retinal Antigen	Treatment for Cancer	Treatment for PR	Visual Prognosis	Overall Prognosis
Campo et al,[13] 1992	72	IV	20/80 OU; central scotomas OU; ERG suppressed	PR 2.0 mo before CA	N/A	XRT to pelvis	Steroids	No improvement; later HM OU	Died 6 mo after diagnosis
Brink et al,[14] 1997	67	IV	VA 0.3 OU; retinal detachments OU	CA 1 y before PR	N/A	TAHBSO, medroxyprogesterone	XRT (30 Gy) OU	No improvement; later HM OU	Died 4 mo after PR
Sekiguchi et al,[6] 1998	60	IB	VA 0.1 OU; suppressed ERG	PR 4.0 mo before CA	(+) 34 kDa	TAHBSO, later chemo on POD	Steroid eyedrops	No improvement; later HM OU	Died 2 y after diagnosis from metastases
Adamus and MacKay,[8] 1998	61	IV	20/70 OD; CF OS	CA 3.0 mo before PR	(+) Recoverin	TAHBSO, XRT and chemo, megestrol acetate, 714X (experimental drug)	Steroids, plasmapheresis, Tolpa Torf Preparation	Transient improvements; stable at HM	
Ju et al,[15] 2005	57	IV	Decreased VA; suppressed ERG	PR 1.5 mo before CA	N/A	XRT to spine metastasis	N/A	N/A	N/A
Present case	61	IV	–19.86 dB OD and –25.13 dB OS VA	PR 1.5 mo before CA	Negative	TAHBSO, chemo	Steroids, IVIG, rituximab	Stable	Died 18 mo after diagnosis

Abbreviations: CA, cancer; CF, counting fingers; chemo, chemotherapy; ERG, electroretinography; HM, hand movement; IVIG, intravenous immunoglobulin; N/A, not applicable; OD, right eye; OS, left eye; OU, both eyes; POD, progression of disease; PR, paraneoplastic retinopathy; TAHBSO, total abdominal hysterectomy bilateral salpingo-oophorectomy; VA, visual acuity; XRT, chemoradiation.

The success of rituximab in treating autoimmune disorders warrants further exploration of the drug, and a phase I study is underway to determine the effectiveness of rituximab in treating autoimmune retinopathy (ClinicalTrials.gov identifier: NCT01086631).

References

1. Khan N, Huang JJ, Foster CS. Cancer associated retinopathy (CAR): an autoimmune mediated paraneoplastic syndrome. Semin Ophthalmol 2006;21:135–141.
2. Sawyer RA, Selhorst JB, Zimmerman LE, et al. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol 1976;181:606–613.
3. Chan JW. Paraneoplastic retinopathies and optic neuropathies. Surv Ophthalmol 2003;48:12–36.
4. Jacobson DM, Thirkill CE, Tipping SJ. A clinical triad to diagnose paraneoplastic retinopathy. Ann Neurol 1990;28:162–167.
5. Eltabbakh GH, Hoogerland DL, Kay MC. Paraneoplastic retinopathy associated with uterine sarcoma. Gynecol Oncol 1995;58:120–123.
6. Sekiguchi I, Suzuki M, Sato I, et al. Rare case of small cell carcinoma arising from the endometrium with paraneoplastic retinopathy. Gynecol Oncol 1998;71:454–457.
7. Guy J, Aptsiarui N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin. Arch Ophthalmol 1999;127:612–614.
8. Adamus G, MacKay C. Long term persistence of anti-recoverin antibodies in endometrial cancer-associated retinopathy. Arch Ophthalmol 1998;116:251–253.
9. Espander L, O'Brien S, Thirkill C, et al. Successful treatment of cancer-associated retinopathy with alemtuzumab. J Neurooncol 2007;83:295–302.
10. Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol 2009;9:10–25.
11. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease—the immune complex decoy hypothesis. Nat Clin Pract Rheumatol 2007;3:86–95.
12. Adamus G, Ren G, Weleber RG. Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. BMC Ophthalmol 2004;4:5.
13. Campo E, Brunier MN, Merino MJ. Small cell carcinoma of the endometrium with associated ocular paraneoplastic syndrome. Cancer 1992;69:2283–2288.
14. Brink H, Deutman A, Beex L. Unusual retinal pigment epitheliopathy and choroidopathy in carcinomatosis: a rare case of cancer-associated retinopathy. Graefe's Arch Clin Exp Ophthalmol 1997;235:59–61.
15. Ju W, Park IA, Kim SH, et al. Small cell carcinoma of the uterine corpus manifesting with visual dysfunction. Gynecol Oncol 2005;99:504–506.

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/31860;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. Recoverin, a 23-kDA retinal protein is the most common antigen associated with cancer-associated retinopathy.
   a. True
   b. False
2. Rituximab is a monoclonal antibody directed against CD20, and is used in the treatment of B-cell non-Hodgkin's lymphoma and multiple autoimmune diseases. Possible mechanisms of action for rituximab include:
   a. Complement-dependent cytotoxicity
   b. Antibody-dependent cellular cytotoxicity
   c. Increased phagocytosis through reticulo-endothelial system
   d. Induction of direct cell death (apoptosis)
   e. All of the above
3. Visual symptoms in cancer-associated retinopathy always correlate with the systemic disease burden and response of the systemic disease to chemotherapy or other therapies directed against the primary cancer.
   a. True
   b. False