American Journal of Ophthalmology Case Reports 2 (2016) 4–7

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: http://www.ajocasereports.com/

Case report

Electroretinographic improvement after rituximab therapy in a patient with autoimmune retinopathy

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ARTICLE INFO

Article history:
Received 28 January 2016
Received in revised form
20 March 2016
Accepted 26 March 2016
Available online 30 March 2016

Keywords:
Autoimmune retinopathy
Nonparaneoplastic
Neoplastic
Rituximab
Electroretinography
Electrophysiology

ABSTRACT

Purpose: To describe the effect of rituximab on full-field electroretinography (ERG) in a patient with nonparaneoplastic autoimmune retinopathy (npAIR).

Observations: A 58-year-old male patient with visual complaints, positive anti-retinal antibodies and negative work-up for cancer was diagnosed with npAIR. Visual acuity and ancillary tests were normal except abnormal ERG in both eyes. The patient was given one course of rituximab 375 mg/m^2/week for 4 weeks and cyclophosphamide 1 gr/m^2/month for 6 months. A second course of rituximab was necessary as autoantibody titers showed no change and as new antibodies were noted after treatment with rituximab and cyclophosphamide. Electroretinography was repeated after the first course of rituximab, after cyclophosphamide, and the second course of rituximab therapy.

Conclusions and importance: Rituximab therapy led to marked improvement in full-field ERG readings and regression of symptoms was reported by the patient after rituximab infusions. The effect of rituximab in npAIR was objectively demonstrated with ERG.

1. Introduction

Autoimmune retinopathy (AIR) is an immune-mediated retinal degeneration characterized by progressive vision loss, abnormal electroretinography (ERG), visual field deficits, and presence of circulating anti-retinal autoantibodies. Two forms of AIR exists: paraneoplastic (pAIR) and nonparaneoplastic (npAIR). Paraneoplastic AIR is further subdivided into cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) [1–5]. Lymphoma associated retinopathy (LAR) has also been described [6–8]. Nonparaneoplastic AIR is more common than pAIR [1,3,4]. Patients with npAIR are mostly female and have a history and/or family history of autoimmune disease [1–4].

The diagnosis of AIR should be considered in patients with subacute vision loss, photopsias, nyctalopia, scotomas, photoaversion, dyschromatopsia and/or visual field loss [1–5]. Some patients may also have diminished central vision and loss of contrast sensitivity [4]. Symptoms are usually bilateral, but can be asymmetric between the eyes [1–5]. Visual acuity may be deceivingly good in the early stages of the disease [1]. The fundus can appear unremarkable initially and demonstrate retinal vascular attenuation, diffuse retinal atrophy, retinal pigment epithelium abnormalities, and/or disc pallor later in the disease course [1–5]. Usually, there is no or minimal intraocular inflammation [1–5]. The mean age of onset ranges between 55 and 65 years, with npAIR having a younger age of onset than pAIR [2].

Because of the presumed autoimmune nature of AIRs immunomodulatory agents have been used in an attempt to treat the disease. It is uncertain whether treatment significantly alters the natural course of the disease [1]. More favorable treatment results are achieved in pAIR, particularly CAR [1]. An early attempt to treat AIRs is suggested to end-up with a beneficial outcome [1,9].

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http://dx.doi.org/10.1016/j.ajoc.2016.03.007

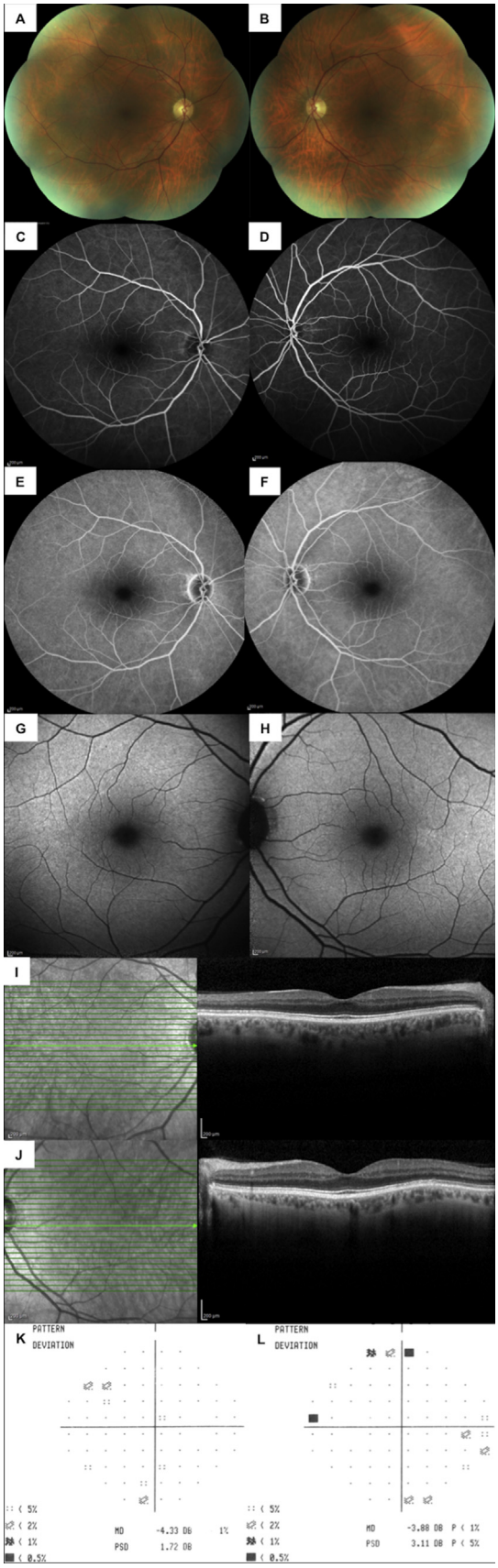

Fig. 1. Color fundus photograph of the right (A) and left eye (B) show attenuated retinal vessels more prominent in the retinal arteries than in retinal veins. Fluorescein angiography shows no abnormal fluorescence in the early (C, D) and late frames (E, F) in the right and left eye. Fundus autofluorescence shows normal autofluorescence in the right (G) and left eye (H). Spectral-domain optical coherence tomography of the right (I) and left eye (J) shows normal inner and outer retinal architecture. Pattern deviation plot of visual field testing with 30-2 Swedish Interactive Thresholding Algorithm (SITA) Fast program of the Humphrey Field Analyzer is within normal limits in the right (K) and left eye (L).

2. Case report

A 58-year-old male patient was referred to the oncology department in August 2014 with a preliminary diagnosis of CAR due to abnormal full-field ERG and elevated cancer antigen (CA) 15-3. The patient was complaining of seeing a peripheral white halo when passing from dark to light and vision fading of colors more prominent in his right eye, for 5 months. He had systemic hypertension and liver hemangiomas. He denied smoking and family history of cancer and autoimmune disease.

Work-up revealed microangiopathic gliosis on cranial magnetic resonance imaging (MRI), hepatic hemangiomas on abdominal MRI (stable when compared with the abdominal MRI taken in 2012), and a normal esophagogastroduedenoscopy and colonoscopy. Complete blood count, serum biochemistry, free/total prostate specific antigen, CA 19-9, carcinoembriogenic antigen, and alpha-fetoprotein were normal. Repeat CA15-3 was positive at 30.4 U/mL (normal: 0–25 U/mL). Ultrasound of subareolar breast tissue was normal. Positron emission tomography/computed tomography showed no hypermetabolic activity.

Ophthalmologic examination showed a best-corrected visual acuity of 1.0 in both eyes. Pupils were equal and reactive to light; there was no relative afferent pupillary defect. Biomicroscopy was unremarkable in both eyes. Intraocular pressures were 16 mmHg in both eyes. Fundus examination showed attenuated retinal vessels more prominent in the retinal arteries than in retinal veins bilaterally (Fig. 1A, B). Fluorescein angiography, fundus autofluorescence, spectral-domain optical coherence tomography (SD OCT), and computerized perimetry were normal in both eyes (Fig. 1C–L). Full-field ERG and pattern visual evoked potentials (VEP) and ERG were conducted in October 2014 (Table 1). Western blot analyses at Casey Eye Institute Ocular Immunology Laboratory showed anti-retinal autoantibodies against 23-kDa (not reactive to recoverin), 42-kDa, and 70-kDa proteins and anti-optic nerve autoantibody against 35-kDa protein. A diagnosis of npAIR was established based on the patient's visual symptoms, abnormal full-field ERG, and the presence of anti-retinal autoantibodies. A treatment protocol consisting of 4 cycles of rituximab 375 mg/m^2/week, followed by 6 cycles of cyclophosphamide 1 gr/m^2/month was planed. Electroretinography was repeated after 4 cycles of rituximab infusions before cyclophosphamide was begun and after the 6 cycles of cyclophosphamide therapy. Despite remaining subnormal a marked improvement in full-field ERG parameters was recorded 3 weeks after the course of rituximab and before cyclophosphamide treatment in February 2015 (Table 1). The patient reported recovery in visual symptoms after the third cycle of rituximab infusion.

After completion of 6 cycles of intravenous pulse cyclophosphamide therapy full-field ERG was repeated in August 2015 (Table 1) and blood was send to Casey Eye Institute Ocular Immunology Laboratory for re-evaluation. Although full-field ERG readings showed a decline when compared to post-rituximab, readings were still better than baseline. Anti-retinal antibody testing showed positivity of 23-kDa (not reactive to recoverin), 36-kDa (GADPH), 40-kDa (aldolase), and 42-kDa with no significant change in previous antibody titers and presence of new autoantibodies. Also were noted new anti-optic nerve antibodies against 19-kDa, 21-kDa, 23-kDa, 35-kDa and 136-kDa proteins.

Table 1
Electrophysiological test readings of the patient at baseline and following each immunomodulatory agent given.

Electrophysiological test	Eye	Baseline Oct 2014	RTX Feb 2015	CYC Aug 2015	RTX Dec 2015	Normal range
Full-field ERG						
DA 0.01 (b-wave)	Right	5.08	*1.46*	**10.4**	**16.8**	117-224
(amplitude, μV)	Left	1.07	**7.13**	**12.3**	**20.0**	
DA 3.0 (a-wave)	Right	2.34	**101**	**15.1**	**86.1**	156-273
(amplitude, μV)	Left	36.2	**119**	**106**	**135**	
DA 3.0 (b-wave)	Right	0.68	**146**	1.95	**78.6**	311-592
(amplitude, μV)	Left	97.9	*80.7*	**151**	**203**	
Oscillatory potentials	Right	2.77	**30.6**	**13.7**	**12.7**	22-51
(amplitude, μV)	Left	3.09	**16.1**	**19.9**	**30.3**	
LA 3.0 (a-wave)	Right	0.48	**14.2**	**7.13**	**7.52**	27-35
(amplitude, μV)	Left	11.5	**22.5**	**16.6**	**17.5**	
LA 3.0 (b-wave)	Right	6.93	**12.2**	*6.54*	**16.3**	88-209
(amplitude, μV)	Left	40.1	**57.7**	**48.5**	**48.1**	
LA 3.0 30 Hz Flicker	Right	7.52	**12.4**	**15.2**	**17.1**	66-152
(amplitude, μV)	Left	38.5	**39.4**	**41.3**	**43.9**	
LA 3.0 30 Hz Flicker	Right	58.8	47.8	63.3	58.8	60-64.2
(implicit time, ms)	Left	63.3	*65.2*	62.6	62.6	
Pattern VEP						
P100	Right	101.6	*129.7*	104.5	*122.7*	90-120
(latency,ms)	Left	118.6	*129.7*	117.4	117.4	
N75-P100	Right	6.41	4.32	6.05	3.70	1-8
(amplitude, μV)	Left	5.82	4.32	4.55	3.19	
Pattern ERG						
N35	Right	31	32.1	31.4	31.7	25-45
(latency, ms)	Left	31	32.1	31.4	31.4	
P50	Right	56.7	54.2	56.4	56.7	40-60
(latency, ms)	Left	53.9	58.1	55.3	55.7	
N95	Right	102.9	*116.2*	103.6	102.5	85-105
(latency, ms)	Left	102.5	*113.8*	102.9	102.9	

ERG: electroretinography; DA: dark adopted; LA: light adopted; VEP: visual evoked potentials; RTX: after a course of 4 cycles of rituximab 375 mg/m^2/week; CYC: after a course of 6 cycles of cyclophosphamide 1 gr/m^2/month; Bold characters: Improvement compared to baseline reading, Italic characters: Worsening compared to baseline reading, Red characters: Normal reading

Upon receiving the auto-antibody results the patient was given a second course of 4 cycles of rituximab therapy (375 mg/m^2/week). Post-therapy ERG in December 2015 showed a marked improvement in ERG with the most prominent changes occurring in dark adapted 3.0 a- and b-waves showing combined rod-cone response and oscillatory potentials indicating inner retinal function (Table 1). The patient reported recovery in visual symptoms after the second course of rituximab as well. A third blood sample obtained after the second course of rituximab therapy showed positive anti-retinal autoantibodies against 23-kDa (not reactive to recoverin), 40-kDa (aldolase), 42-kDa, and 62-kDa proteins and anti-optic nerve autoantibodies against 21-kDa, 23-kDa, 30-kDa, 40-kDa, and 136-kDa proteins. The laboratory reported no significant change since the last testing.

The patient's complete blood count was followed along treatment. Lymphocyte count was 2500/μL (normal range: 1000–7000/μL) at baseline and decreased to 1800/μL immediately after the 4th cycle of rituximab before cyclophosphamide was begun, 1100/μL after completion of cyclophosphamide therapy before the second course of rituximab and remained at 1100/μL immediately after the 4th cycle of second course of rituximab.

The patient was re-surveyed for cancer development in August 2015 and PET/CT was negative for malignancy. Cancer antigen 15-3 was re-detected at 31.6 U/mL (normal: 0–25 U/mL). Regular ophthalmological follow-up examinations were stable and repeat SD OCT and computerized perimetry remained normal.

This report was deemed exempt from institutional review board approval and an informed consent was obtained from the patient.

3. Discussion

Treatment options for AIRs are systemic and local corticosteroids, plasmapheresis, intravenous immunoglobulin, and conventional immunomodulatory therapy with azathioprine, mycophenolate mofetil, and cyclosporine A [1–5,9]. Rituximab is a monoclonal antibody against CD20 expressed on B cells and was originally developed for the treatment of non-Hodgkin's B-cell lymphoma. In the last several years B-cell targeting therapies were approved for the treatment of autoimmune diseases. Rituximab depletes B-cells by antibody and complement-dependent cytotoxicity and stimulation of apoptotic pathways. The cell surface glycoprotein CD20 is expressed on B-cells from early development in the bone marrow until terminal differentiation to plasma cells. Therefore, rituximab depletes immature and mature B-cells from blood and tissue and does not eliminate long-lived plasma cells that are the main source of antibodies [10]. Presence of anti-retinal antibodies and an abnormal ERG is crucial in establishing the diagnosis of AIRs [1–5]. Rituximab treatment effectively stabilized or improved visual acuity in three separate case reports on AIR [11–13]. In only one of the reports serum testing was repeated after rituximab therapy and showed a decline in the immunoreactivity against human retina by indirect immunohistochemistry [11]. In the remaining two reports repeat serum testing to assess for a change in anti-retinal antibodies following rituximab therapy was not studied. Serum anti-retinal and anti-optic nerve antibodies did not decline and there was even occurrence of new antibodies in the post-therapy serum samples of the patient reported herein who

was tested twice over the treatment course. Besides its diagnostic role electroretinography is also used as an indicator for treatment response [1,4,9]. Post-therapy ERG has not been done in the rituximab treated AIR cases [11–13]. In our case full-field ERG responses showed marked improvement after the 1st and 2nd course of rituximab therapy given as 4 cycles at a dose of 375 mg/m^2/week. There was also recovery in the patient's symptoms reported to occur immediately after the rituximab infusions. Although we were able to document a marked improvement of full-field ERG after rituximab infusions, we could not demonstrate a decline or negativity of auto-antibodies following treatment with rituximab. We speculate that it might be related to the persistence of plasma cells despite presence of rituximab induced altered humoral immunity. Although a decrease or negativity of auto-antibodies following treatment with other immunomodulatory agents has been reported, the significance of this finding is unclear as anti-retinal antibodies have a broad range of specificity and heterogeneity and as the pathogenic mechanisms of retinopathies are complex [1,14].

Non-paraneoplastic AIR with presence of retinal and optic nerve autoantibodies is called autoimmune-related retinopathy and optic neuropathy (ARRON) [15,16]. Despite lack of optic disc staining in fluorescein angiography and visual field defect(s) that would indicate optic nerve involvement, our patient had positive anti-optic nerve antibody initially and the presence of new anti-optic nerve antibodies were noted in the second and third blood samples. A worsening in pattern VEP and ERG (N95 latency signifying ganglion cell function) was observed after the first course of rituximab. There is no report on VEP and pattern ERG in ARRON. Despite presence of new anti-optic nerve antibodies, an abnormality did not occur in follow-up pattern VEP examinations and an abnormal reading was only documented in the worse right eye of the patient at the final electrophysiological evaluation in December 2015. We hypothesize that optic nerve function may not improve after therapy in ARRON as seen in demyelinating optic neuropathies [17].

Although recoverin, a 23-kDa calcium-binding protein found on photoreceptors, and α-enolase, a-46 kDa ubiquitous glycolytic enzyme, are the most widely studied antigens in AIR, other autoantibodies including those against carbonic anhydrase, arrestin, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), aldolase, transducing-β, TULP1, neurofilament protein, heat shock protein-70, photoreceptor-cell-specific nuclear receptor, Müller-cell-specific antigen, transient receptor potential cation channel, subfamily M, member 1 (TRPM1), and a number of antigens that are still unidentified were studied [2]. Most patients with AIR symptoms and signs have multiple bands of anti-retinal antibodies on Western blot with the majority showing a minimum of three different bands as in our case [4]. In our patient the diagnosis of npAIR was established based on positive anti-retinal antibodies on Western blot against 23-kDa, 42-kDa, and 70-kDa proteins. The 23-kDa protein did not correspond to anti-recoverin antibody. Although recoverin has been historically shown to be a target antigen in CAR the incidence of anti-recoverin antibodies in CAR is very low across different kinds of tumor and ranges between 3% and 5% [18].

Despite a positive CA15-3, which is not a sensitive tumor marker per se, the patient's work-up revealed no cancer [19]. However, the patient remains as a suspect for CAR, as the patient is 58-year-old, of male gender, has no history and/or family history of autoimmune disease, and as autoantibodies may precede cancer development in pAIR. Continued surveillance for malignancy appears mandatory in the follow-up of the patient. The patient reported herein represents electroretinographic evidence for the successful treatment of AIR with rituximab.

References

[1] L. Grange, M. Dalal, R.B. Nussenblatt, H.N. Sen, Autoimmune retinopathy, Am. J. Ophthalmol. 157 (2014) 266–272.
[2] F. Forooghian, S. Cao, J. Cui, J.A. Matsubara, The enigma of autoimmune retinopathy, Int. Ophthalmol. Clin. 55 (2015) 81–91.
[3] E. Rahimy, D. Sarraf, Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management, Surv. Ophthalmol. 58 (2013) 430–458.
[4] J.R. Heckenlively, H.A. Ferreyra, Autoimmune retinopathy: a review and summary, Semin. Immunopathol. 30 (2008) 127–134.
[5] Y. Shildkrot, L. Sobrin, E.S. Gragoudas, Cancer-associated retinopathy: update on pathogenesis and therapy, Semin. Ophthalmol. 26 (2011) 321–328.
[6] K.W. To, C.E. Thirkill, F.A. Jakobiec, S. Lessell, E.L. Berson, Lymphoma-associated retinopathy, Ophthalmology 109 (2002) 2149–2153.
[7] K. Ohta, A. Yoshida, A. Sato, E. Fukui, T. Kikuchi, Retinal involvement in uveitis associated with Hodgkin disease, Retin Cases Brief. Rep. 8 (2014) 17–20.
[8] K.V. Bhavsar, T. Hedges, C.E. Thirkill, E. Reichel, Paraneoplastic retinopathy associated with systemic follicular cell lymphoma, Ophthalmic Surg. Lasers Imaging Retina 46 (2015) 373–376.
[9] H.A. Ferreyra, T. Jayasundera, N.W. Khan, S. He, Y. Lu, J.R. Heckenlively, Management of autoimmune retinopathies with immunosuppression, Arch. Ophthalmol. 127 (2009) 390–397.
[10] R.J. Looney, R. Srinivasan, L.H. Calabrese, The effects of rituximab on immunocompetency in patients with autoimmune disease, Arthritis Rheum. 58 (2008) 5–14.
[11] C. Or, D.R. Collins, A.B. Merkur, Y. Wang, C.C. Chan, F. Forooghian, Intravenous rituximab for the treatment of cancer-associated retinopathy, Can. J. Ophthalmol. 48 (2013) 35–38.
[12] I. Dy, R. Chintapatla, I. Preeshagul, D. Becker, Treatment of cancer-associated retinopathy with rituximab, J. Natl. Compr. Cancer Netw. 11 (2013) 1320–1324.
[13] N. Mahdi, L.J. Faia, J. Goodwin, R.B. Nussenblatt, H.N. Sen, A case of autoimmune retinopathy associated with thyroid carcinoma, Ocul. Immunol. Inflamm. 18 (2010) 322–323.
[14] G. Adamus, G. Ren, R.G. Weleber, Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy, BMC Ophthalmol. 4 (2004) 5.
[15] Y. Oyama, R.K. Burt, C. Thirkill, E. Hanna, K. Merrill, J. Keltner, A case of autoimmune-related retinopathy and optic neuropathy syndrome treated by autologous nonmyeloablative hematopoietic stem cell transplantation, J. Neuroophthalmol. 29 (2009) 43–49.
[16] J.L. Keltner, C.E. Thirkill, P.M. Huynh, Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome (Abstract), J. Neuroophthalmol. 22 (2002) 160–161.
[17] R.R. Hidajat, D.H. Goode, Normalisation of visual evoked potentials after optic neuritis, Doc. Ophthalmol. 106 (2003) 305–309.
[18] G. Adamus, Latest updates on antiretinal autoantibodies associated with vision loss and breast cancer, Invest. Ophthalmol. Vis. Sci. 56 (2015) 1680–1688.
[19] L. Harris, H. Fritsche, R. Mennel, L. Norton, P. Ravdin, S. Taube, M.R. Somerfield, D.F. Hayes, R.C. Bast, American Society of Clinical Oncology, American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer, J. Clin. Oncol. 25 (2007) 5287–5312.