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Bilateral paraneoplastic optic neuropathy and unilateral retinal compromise in association with prostate cancer: a differential diagnostic challenge in a patient with unexplained visual loss

Giovannella Carboni,

Retinal Degeneration and Ophthalmic Genetics Service, Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 731, Memphis, TN 38163, USA

Gina Forma,

Retinal Degeneration and Ophthalmic Genetics Service, Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 731, Memphis, TN 38163, USA

April D. Bond,

Retinal Degeneration and Ophthalmic Genetics Service, Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 731, Memphis, TN 38163, USA

Grazyna Adamus, and

Ocular Immunology Laboratory, Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA

Alessandro Iannaccone

Retinal Degeneration and Ophthalmic Genetics Service, Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 731, Memphis, TN 38163, USA

Alessandro Iannaccone: aiannacc@uthsc.edu

Abstract

We report a 77-year-old Caucasian man with a 1-year complaint of unexplained visual loss and a 4-year history of prostate cancer. A complete ophthalmologic exam, Goldmann visual fields (GVFs), intravenous fluorescein angiography (IVFA), macular and disc optical coherence tomography (OCT), pattern-reversal visual evoked potentials (PVEPs), and flash electroretinograms (ERGs) were performed. On examination, visual acuity was reduced bilaterally. Fundus exam showed juxtapapillary changes (OS > OD) and, in OS, disc pallor, peripheral RPE dropout and whitish retinal discoloration along the arcades. OCTs were normal OU. Cancer-associated retinopathy (CAR) was suspected. A flash ERG was normal OD and markedly reduced and electronegative OS. An IVFA showed bilateral juxtapapillary staining and changes highly suggestive of sequelae of central retinal artery occlusion (CRAO) OS, in which a cilioretinal artery existed along the papillomacular bundle. GVFs showed bilateral blind spot enlargement and centrocecal scotomas, and PVEPs were delayed. These findings suggested

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Correspondence to: Alessandro Iannaccone, aiannacc@uthsc.edu.

Present Address: G. Carboni, G. Forma, Institute of Ophthalmology, S. Giovanni di Dio Hospital, University of Cagliari, Cagliari, Italy

Present Address: A. D. Bond, Medtronic Corp., Memphis, TN, USA

cancer-associated optic neuropathy (CAON), confirmed by presence of anti-optic nerve autoantibodies (auto-Abs). No anti-retinal auto-Abs were found. CAON is a less common paraneoplastic manifestation than CAR and it is rarely observed in association with prostate cancer. A combination of visual function testing methods permitted the recognition, in this highly unusual case, of the concurrent presence of unilateral ERG changes most likely attributable to CRAO complications in OS, in all likelihood unrelated to CAON, and not to be confused with unilateral CAR. Auto-Ab testing in combination with visual function tests helps achieve a better understanding of the pathophysiology of vision loss in paraneoplastic visual syndromes.

Keywords

Electroretinogram; Visual evoked potentials; Visual field; Central retinal artery occlusion; Paraneoplastic optic neuropathy; Autoimmunity

Purpose

Unexplained visual loss is a common reason for referrals to visual function diagnostic laboratories. This is especially the case when fundus exam may be normal, or scarce of findings that may explain the complaints presented by patients, which may raise questions about the organic nature of the visual symptoms that they are experiencing. Here, we present the case of an elderly man who presented with a subacute history of visual acuity decline and a variety of other visual symptoms (night blindness, light aversion, photopsias, and peripheral visual field reduction) illustrated below that posed a substantial differential diagnostic challenge. We will illustrate how, utilizing a combination of visual function testing methods and targeted serologies for anti-retinal and anti-optic nerve auto-antibodies (auto-Abs) we were able to discover the concurrent presence of apparent sequelae of a vascular complication in the left eye (OS) primarily consistent with the diagnosis of central retinal artery occlusion (CRAO). This was in all likelihood the event that initiated the visual complaints of the patient, yet a serendipitous finding in the context of a bilateral and unrelated case of cancer-associated optic neuropathy (CAON) in a patient with history of prostate cancer confirmed by auto-Ab testing.

Methods

A Caucasian male was first referred to us at the age of 76 years old with a one-year history of progressive bilateral visual acuity loss that had started first in OS, night blindness, light aversion, photopsias, and peripheral visual field reduction. Before being referred to us, he had undergone successful cataract extraction followed by YAG laser capsulotomy in OS, neither one of which improved his vision—which was in fact reported as progressively deteriorating over this period of time also in the right eye (OD). The patient's medical history was mainly significant for the diagnosis of prostate cancer at age 72 and a period of 4 months prior to our first examination during which he was reported by his family to be increasingly confused and somewhat disoriented. He also had history of previous removal of benign skin cancers. Optical coherence tomography (OCT) of the macula had been obtained by the referring physician and excluded either anatomical macular damage or post-operative cystoid macular edema as the possible cause for the progressive vision loss. Magnetic resonance imaging (MRI) of the brain had also excluded any intracranial cause for the vision loss but had identified mild atrophic cortical changes that were attributed to aging.

Our examination included visual acuity with ET-DRS charts, color vision with D15 Panel test, performed with a standard daylight illuminator, anterior segment exam, and dilated fundus biomicroscopy. Imaging studies included digital intravenous fluorescein angiography

(IVFA) and macular and optic nerve spectral domain optical coherence tomography (SD-OCT) inclusive of retinal nerve fiber layer (RNFL) analysis according to standard procedures (Cirrus, Zeiss Meditec, Dublin, CA). Functional testing included Goldmann visual fields (GVFs), pattern-reversal visual evoked potentials (PVEPs), and flash electroretinograms (ERG). In brief, GVFs were performed in response to V4e, III4e and I4e stimuli according to a standard, not-seen to seen testing procedure, following 2 min of adaptation of each eye of the patient to the Goldmann background light [1–3]. PVEPs were elicited monocularly as previously reported in response to checkerboard stimuli of maximal contrast, 1.4-Hz temporal frequency, at four spatial frequencies of decreasing stimulus sizes (90, 45, 22, and 11 min arc, mean luminance: 50 cd/m²) [4]. The recording electrode was placed 3 cm above theinion, the reference electrode on the forehead, and the ground electrode on the right earlobe. Responses were recorded up to three consecutive sessions to verify reproducibility of the signals. The patient wore his best spectacle correction for PVEP testing [4]. Full-field ERG testing was performed after 30 min of full dark-adaptation and maximal pharmacological pupil dilatation. Dark-adapted rod-driven responses were recorded with a $-2.1 \log$ candela [cd]-s/m² white strobe flash, followed by a 0.32 cd-s/m² white flash stimulation in the dark-adapted state to record the mixed rod-cone ERG and in the light-adapted state (steady background of approximately 45 cd/m²) to measure cone-driven ERGs (1.4-Hz transient and 29-Hz flicker) [5, 6]. Corneal ERG-Jet electrodes were used to measure the responses and were applied following topical anesthesia. Reference and ground electrodes were applied on the forehead and the right earlobe, respectively.

Subsequent to the functional work-up, the patient underwent diagnostic serum Western blots against homogenates of human donor retinas and retrobulbar portions of the optic nerve for anti-retinal and anti-optic nerve auto-Abs, respectively, and immunohistochemistry (IHC) on human donor tissue for localization of the autoreactivity at the cellular level in the retina, according to recently reported methods [7].

Results

At our baseline examination, best-corrected visual acuity at baseline was 20/70 OD and 20/80 OS. This represented an additional decrease from a reading, obtained 1 month earlier by the referring physician, of 20/60 and 20/50. Five months after the baseline visit, the patient's visual acuity had decreased further to 20/160 in both eyes. Color vision testing with the Panel D-15 showed a mixed acquired color vision defect, OS > OD (not shown). Anterior segment exam showed mild cataracts OD and pseudophakia OS. Intraocular pressures were 10 mmHg in both eyes. Dilated fundus examination showed (Fig. 1a–b) juxtapapillary atrophy on the temporal aspect of the disc OU and pigmentary changes supero-temporally to the disc margin OD. In addition, compared to OD, OS was remarkable for vascular attenuation and sheathings, peripheral RPE dropout, and whitish retinal discoloration along the arcades.

A Goldmann visual field (Fig. 2a) showed enlarged blind spots OU and bilaterally depressed pericentral sensitivity, more severe OD. In OD, there was also a bundle-like area of uncertain detection of the I4e target, which was moderately constricted in size OU. Relative central sparing was present OU, with a small island of I4e detection in OD and a band-shaped area of I4e detection along the papillomacular bundle in OS. These findings were highly suggestive of an optic neuropathy.

Pattern-reversal VEPs (Fig. 2b) revealed progressively smaller amplitudes and progressively more delayed timing in both eyes as a function of decreasing stimulus size. Consistent with the Goldmann visual field findings, VEPs were more severely compromised OD. These

findings further confirmed the suspicion of a bilateral optic neuropathy, but did not entirely allow us to rule out a retinopathy affecting primarily the posterior pole.

After 30 min of dark-adaptation, flash ERGs were performed (Fig. 2c). Somewhat surprisingly, findings were completely normal OD, but were all markedly diminished OS. Particularly, the mixed rod-cone dark-adapted ERG showed a reduction of the a-wave by about 50 % compared to OD and a virtually absent b-wave (electronegative response). This finding was suggestive of possible sequelae of central retinal artery occlusion (CRAO) OS, or of an otherwise unilateral retinopathy OS.

An IVFA was therefore performed. The early phases of the angiogram showed clearly the presence of a cilio-retinal artery OS that filled before the retinal circulation (Fig. 1c). Later phases showed bilateral staining on the temporal aspect of the disc (Fig. 1d–g), corresponding to areas of pigmentary scarring, suggestive of a previous inflammatory event affecting the optic nerves. There was a large area of retinal pigment epithelial window defects and staining along the inferior temporal arcade OS, suggestive of a previous retinal event (Fig. 1d). These retinal changes were not apparent in OD. Macular SD-OCT findings appeared, at this stage, within normal limits, and so was the RNFL of the optic disc (not shown).

At this stage of the work-up of this patient, it was concluded that the most probable explanation for the progressive visual loss was a bilateral optic neuropathy. The ERG findings were interpreted essentially as incidental, most likely subsequent to sequelae of CRAO that had probably occurred shortly after the cataract surgery OS but had gone undetected (and with far less serious visual loss sequelae than usual) because of the serendipitous presence of a cilio-retinal artery that mitigated significantly the resulting degree of visual loss OS. The presence of the cilio-retinal artery explained well also the horizontal band of preserved central sensitivity to the I4e in OS on Goldmann visual field testing (Fig. 2a). However, at this stage of the work-up, the possibility of a unilateral retinopathy of non-vascular etiology could not yet be entirely excluded. In consideration of the history of prostate cancer, the suspicion of a bilateral CAON was raised, with a possible unilateral CAR, and diagnostic testing for anti-retinal and anti-optic nerve auto-Abs was ordered, along with retinal IHC.

Retinal IHC showed no staining of the human donor retinal tissue. Western blots were negative for anti-retinal auto-Abs, including no reactivity against common retinal proteins involved in retinal autoimmunity such as recoverin and α -enolase, but it was positive for the anti-optic nerve auto-Abs against an optic nerve 24–26 kDa protein complex. These findings further argued in favor of the working diagnosis of bilateral CAON and of the incidental diagnosis of sequelae, in the left eye, of CRAO mitigated by the presence of a cilioretinal artery, and argued against the diagnosis of unilateral CAR. This case has also been included in a recently reported large series of patients with autoimmune neuro-retinopathies exhibiting auto-Abs that recognize optic nerve antigens (patient 26 in Table 1 of Adamus et al. [7]).

Conclusions

Paraneoplastic visual syndromes are relatively infrequent diseases associated with vision loss caused by retinopathy (CAR) and/or neuropathy (CAON) [8–19]. We have documented a number of cases of autoimmune neuro-retinopathies, a portion of which cancer-associated [20, 21]. Such paraneoplastic syndromes are thought to originate from an autoimmune process directed against cancer and circulating antibodies to specific neuronal antigens have been identified in some cases. While the exact series of events in CAR and CAON is not yet

completely understood, it is believed that the immune system, when cancer is present, mounts a response against antigens expressed by cancerous cells. If these antigens are identical to retinal and/or optic nerve ones, or cross-react with them, the immune system activation can lead accidentally to retinal and/or optic nerve neuronal cell degeneration and death, resulting in vision loss mainly through pro-apoptotic mechanisms [7, 19, 22–27].

CAON is the cause of subacute, progressive, usually bilateral and painless visual loss. The optic disc in patients with CAON can be normal or elevated in appearance early on, but it is reported to eventually develop pallor [22]. Visual loss in CAON usually occurs over weeks or months, and central or paracentral visual field scotomas, decreased color vision, and abnormal VEPs are usually demonstrated in affected patients [21, 28]. CAON has also been reported as part of more widespread neurological paraneoplastic brainstem or cerebellar syndromes in patients with a variety of cancers [27, 29]. Most of these cases present with bilateral optic disc edema that reportedly improve with cancer treatment. In contrast, other cases of paraneoplastic syndromes develop years after the original cancer. Neuropathological post-mortem findings in these patients range from nonspecific perivascular inflammation, axonal loss or demyelination of the optic nerve, brainstem gliosis and glial nodule formation and avascular periaxonal lymphocytic infiltration around multiple cerebral nuclei, pons, and substantia nigra [27, 29, 30].

Paraneoplastic syndromes in association with prostate cancer are common, and second only to renal cell carcinoma among urological malignancies [31]. However, prostate cancer accounted for only 7 % of the causes of CAR in a large series [19], paraneoplastic neurological syndromes in association with this kind of cancer are very rare [32] and, to the best of our knowledge, no case of CAON in conjunction with prostate cancer has been reported in detail to date. In our recently reported case series of patients exhibiting auto-Abs recognizing optic nerve antigens, four of 30 cases (13 %) were in association with prostate cancer [7]. Of note, three of four exhibited reactivity *only* against optic nerve antigens [7], which suggests that CAON may be the most common type of paraneoplastic visual loss associated with prostate cancer.

The differential diagnosis of this case was particularly challenging since this was not a simple case of CAON, but one complicated by the simultaneous (and, in our opinion, unrelated and serendipitous) presence of CRAO sequelae and absence of demonstrable CAR, which is the most typical of the paraneoplastic ocular manifestations. We propose that, in this patient, the diagnosis of CRAO after the cataract surgery in OS went undetected because of the presence of the cilio-retinal artery, which mitigated significantly the severity of the initially unilateral visual loss, which was followed by bilateral progressive visual loss once CAON developed.

Our diagnosis of CRAO sequelae is not a diagnosis of certainty, since 1 year after the onset of visual loss OS, there was no clear-cut evidence of arterial non-perfusion or diffuse retinal whitening as one would expect in acute or recent-onset CRAO. However, the diagnosis of sequelae of CRAO is strongly supported by the ERG findings in OS (which are typical for CRAO) [33] vis-à-vis the perfectly normal ERG responses in OD, and indirectly supported by the finding of the cilio-retinal artery OS, the absence of anti-retinal auto-Abs, and the normal retinal IHC results. Of course, it must be remembered that the latter two may be related to the presence of auto-reactivity at very low levels and/or against antigens not accessible to IHC stains. With this caveat in mind, even though paraneoplastic involvement of both the retina and the optic nerve is common [7] and interocular asymmetry in clinical and functional findings is a frequent and unexplained finding in our experience with autoimmune neuro-retinopathies [20, 21, 34], unlike CRAOs, we have yet to observe a single case of *entirely* unilateral autoimmune retinal disease (unpublished observation).

Therefore, our findings support best the diagnosis of bilateral CAON in a patient with prostate carcinoma and documented auto-Abs recognizing optic nerve antigens in conjunction with unilateral CRAO.

The diagnosis in this patient was achieved with an array of visual functional and imaging tests, each contributing key information. GVFs and pattern-reversal VEPs were especially important in pointing to the bilateral optic neuropathy subsequently confirmed by auto-Ab testing, but no single test was sufficient to formulate the diagnosis. The benefits of a careful use of visual function tests and the utilization of the information provided by these tests in guiding further diagnostic work-up is underscored by this case, which represented a substantial differential diagnostic challenge in a patient with an otherwise unexplained visual loss.

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Fig. 1.

a, b Color view of the disc area in OD and OS, respectively, showing the juxtapapillary atrophy and pigmentary changes around the disc OU. Compared to OD, vascular attenuation, epipapillary perivascular sheathings (*black arrowheads*), and retinal discoloration along the infero-temporal arcade can also be noted in OS (**b**). **c** Early phase of IVFA: the *arrowhead points* at the cilio-retinal artery in the *left eye*. **d–g**: Middle and late phases of IVFA showing the increasing staining around the discs (*white arrows*) and a large area (*black asterisks*) of mottled hyperfluorescence attributable to a combination of retinal epithelial window defects and intraretinal staining along the inferior temporal arcade in the *left eye*

Fig. 2.

a Goldmann Visual Field of OS and OD, respectively, showing bilateral enlargement of the blind spot and depressed pericentral sensitivity, more severe in OD, where a relative bundle-like scotoma to the I4e target is also present (dotted inferior temporal band). **b** PVEPs show a consistent and progressively more severe delay in both eyes to all stimulus sizes. The *gray bars* indicate the timing's normal range of the P100. **c** The ERG tests are completely normal in OD, while OS shows delayed timing and reduced amplitudes; the *b-wave* is nearly absent in the mixed rod-cone response, and cone and flicker responses are markedly reduced [shown magnified at lower scale in the *inset* to illustrate that they remained nonetheless recordable]. *Vertical calibration bars* are for amplitudes in microvolts (μV), and *horizontal calibration bars* are for response timing in milliseconds (ms). Rod: rod-driven dark-adapted response; Mix: mixed rod/cone-driven dark-adapted response; Cone: cone-driven transient light-adapted response; Flick: cone-driven, light-adapted response to flicker stimuli