Graefe's Archive for Clinical and Experimental Ophthalmology (2022) 260:975–991
https://doi.org/10.1007/s00417-021-05409-4

INFLAMMATORY DISORDERS

Autoimmune retinopathy: clinical, electrophysiological, and immunological features in nine patients with long-term follow-up

Khaled Safadi[1] · Itay Chowers[1] · Eyal Banin[1] · Boris Rosin[1] · Liran Tiosano[1] · Radgonde Amer[1]

Received: 2 October 2020 / Revised: 27 August 2021 / Accepted: 1 September 2021 / Published online: 30 September 2021

Abstract

Purpose We aim to report on the clinical, imaging, immunological, and electrophysiological features of patients with autoimmune retinopathy (AIR) with long-term follow-up.

Methods Single-center, retrospective study of a consecutive group of AIR patients treated in a tertiary academic medical center.

Results Included were nine patients with a mean ± SD age at presentation of 65 ± 13 years and a median follow-up of 63 months (range 18–120). Five patients were known to have cancer. Median interval between onset of ocular symptoms and diagnosis of AIR was 36 months. Mean baseline and final LogMAR visual acuity were 0.72 ± 0.9 and 1.1 ± 1.2, respectively ($p = 0.17$). The most common funduscopic findings included optic atrophy and bone-spicule-like pigmentation. Thinning of the nerve fiber layer was the most frequent optical coherence tomographic abnormality. Electroretinographic (ERG) recordings demonstrated variably reduced cone- and rod-derived amplitudes in the majority of eyes at presentation. The most commonly detected anti-retinal antibody was anti-α-enolase. Treatment included immunomodulatory therapy and plasmapheresis. ERG tests showed stability in 64% of eyes throughout the treatment period.

Conclusion This study highlights the importance of maintaining a high index of suspicion of AIR, particularly in late middle-aged and elderly patients with "unexplained" visual loss, in light of the non-specific posterior segment signs and the inconsistency of the routinely used ancillary tests.

Keywords Autoimmune retinopathy · Paraneoplastic retinopathy · Non-paraneoplastic retinopathy

Key messages

Known key messages

- Autoimmune retinopathy (AIR) is a progressive retinal degeneration caused by autoimmune processes. It is a diagnostic and therapeutic challenge with no established therapeutic protocol to date.

New key messages

- The study shows lack of agreement between the commonly used ancillary tests like visual fields and OCT.
- ERG was demonstrated to be a useful marker for assessing disease progression and response to treatment.
- Throughout the long-term follow-up period, patients exhibited mostly stability of ERG parameters with immunomodulatory therapy.

✉ Radgonde Amer
radgonde@gmail.com

[1] Department of Ophthalmology, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, POB 12000, 91120 Jerusalem, Israel

Introduction

Autoimmune retinopathy (AIR) is a progressive retinal degeneration caused by autoimmune processes. It is characterized by the presence of circulating anti-retinal antibodies (ARA) that are believed to lead to injury of photoreceptors or other neuronal elements in the retina; however, the exact mechanism by which such injury occurs is not entirely understood. AIR is subdivided into paraneoplastic and non-paraneoplastic categories. Paraneoplastic retinopathies (pAIR) include cancer-associated retinopathy (CAR), melanoma-associated retinopathy, and lymphoma-associated retinopathy [1–3].

Non-paraneoplastic retinopathy (*n*) pAIR is composed of a large group of autoimmune retinopathies with features similar to those of CAR, but without a known underlying malignancy. (*n*) pAIR is usually diagnosed at a younger age and is more prevalent in people with a known personal and/or familial history of autoimmune diseases [1, 4–6].

Symptomatology includes acute, chronic, and progressive vision loss associated with photopsia, nyctalopia, color vision defects, and visual field (VF) defects [1, 4, 7, 8].

AIR is difficult to detect on clinical grounds alone since patients often exhibit minimal retinal changes [4, 5, 9]. Therefore, ancillary tests are needed to quantify and confirm the loss of retinal function. Unfortunately, to date, no single gold standard test exists to confirm the diagnosis of AIR, thus requiring multiple tests to support this somewhat elusive diagnosis.

Such ancillary tests include VF tests, optical coherence tomography (OCT) imaging, electroretinography (ERG), and serum ARA testing. VF deficits can manifest as generalized depression, or scotomas that can be central, paracentral, arcuate, or ring-shaped [10]. OCT most commonly shows retinal atrophy and loss of outer retinal bands, such as ellipsoid zone (EZ), the surveillance of which may potentially serve as an indicator of disease progression [5, 11–13]. Full-field ERG (FF-ERG) can be useful in the diagnosis and in monitoring of disease course. Abnormal ERG findings may include suppressed or even extinguished a-waves and/or b-waves, as well as electronegative waveforms. Notably, this reduction in ERG amplitudes can be demonstrated early in the course of disease, while the funduscopic exam is still normal [11, 14]. The presence of circulating serum ARA is helpful for diagnosis; however, the laboratory tests for ARA are not readily available in most ophthalmological settings, and their diagnostic accuracy as a single test is limited [1, 7]. While fluorescein angiography (FA) is unremarkable in most AIR patients, it is nonetheless useful for ruling out other posterior segment pathologies [15].

Long-term immunomodulatory therapy (IMT) is considered the mainstay of treatment [16]. Different regimens of IMT such as corticosteroids [17], plasmapheresis [18], intravenous immunoglobulin [19], cyclosporine, mycophenolate mofetil [6], and rituximab [20] have been used in the treatment of AIR.

The low incidence of this entity combined with difficulty confirming the diagnosis and monitoring the response to treatment makes the management of AIR challenging [5]. While various imaging modalities are helpful in establishing the diagnosis of AIR [13, 21], there is limited information on long-term ERG findings following therapy [20]. The aim of this study is to describe clinical, imaging, immunological, and electrophysiological features of nine patients with AIR over a long-term follow-up.

Methods

This is a single-center, retrospective study of a consecutive group of AIR patients who were treated at a tertiary referral center. The study was approved by the Institutional Review Board and included waiver of informed consent for the chart review. The study was conducted in adherence to the tenets of the Declaration of Helsinki.

Medical history was extracted from the medical records, including ocular and systemic symptoms, personal and family history of autoimmune disorders and malignancies. Ocular findings at the initial and follow-up visits were recorded including best-corrected Snellen's visual acuity (VA), slit-lamp biomicroscopy, tonometry, and ophthalmoscopy. LogMAR (log of the minimum angle of resolution) transformation was used to estimate the change in VA. For the purpose of analysis, VA of $\leq$ 6/60 was defined as severe visual loss, of 6/60 to 6/12 was defined as moderate visual loss and $\geq$ 6/12 was defined as good VA [22]. Results from ancillary tests including spectral-domain OCT (SD-OCT), FA, VF, FF-ERG, and serum ARA testing were obtained. Results of systemic work-up including complete blood count, liver and kidney function tests, erythrocyte sedimentation rate, C-reactive protein, total body Computerized Tomography (CT) were also recorded. Additional tests, including upper and lower gastrointestinal endoscopy and brain magnetic resonance imaging (MRI), were individualized according to each patient's clinical history, risk factors, general physical examination, and preliminary tests.

pAIR was diagnosed based on a suggestive clinical presentation in a patient with previous or present malignancy, abnormal FF-ERG, and positive serum ARA. (*n*) pAIR was diagnosed in the absence of history of malignancy combined with an extensive work-up that failed to reveal an underlying malignancy. For all patients, vision was unaffected before the present illness, and a complete medical and family history failed to suggest a genetic form of retinal degeneration or any other cause for retinopathy.

Western blot testing for serum ARA was performed at the Ocular Immunology Laboratory, Casey Eye Institute, Oregon Health and Science University on a commercial basis. Serum ARA were reported based on the molecular weights (kDa) of the antigenic retinal proteins.

For all patients, a complete International Society for Clinical Electrophysiology of Vision (ISCEV) standard ERG was performed with one modification. When examining the rod response, a dim blue flash (equivalent to the 0.01 cd.s/m^2 as specified by the standard) was employed instead of the dim white flash specified in the ISCEV standard. Recorded FF-ERG parameters included b-wave amplitude of the isolated rod response (dim blue flash, dark adapted), the a-wave and b-wave amplitudes and latency of the mixed rod-cone response (standard bright white flash, dark adapted), and amplitude and implicit time of the 30-Hz cone flicker response (standard bright white flash, light-adapted). The cone 1-Hz responses and the oscillatory potentials were not analyzed in the present study. FF-ERGs were performed in accordance with the ISCEV Standard employing the LKC UTAS 3000 system, and Henkes monopolar contact lens electrodes were used (Gaithersburg, MD)[23]. Treatment regimens and ERG parameters before and after therapy were collected. The FF-ERG responses' amplitudes were reported in microvolts for each eye. ERG responses were considered stable when the reported amplitudes were within 25% of the baseline values [20] and when cone flicker implicit time was within 10% of the baseline value. As there were multiple parameters in the ERG tests, stability or worsening in each ERG test was defined as stability or worsening in 50% of the parameters of that test. The test was determined to be inconclusive when 50% of the parameters were worse and the other 50% were stable or better [20].

Multifocal ERG (MF-ERG) and the electrooculography test were performed in only a minority of patients and their findings were thus not analyzed.

A Heidelberg Spectralis (Heidelberg Engineering; Heidelberg, Germany) SD-OCT system was used to acquire a 30° × 25° 61-line foveal-centered high-speed volume scan (nine averaged images), a foveal-centered 30° × 5° high resolution seven-line scan (25 averaged images), and a single 30° foveal-centered high speed line scan (100 averaged images). Humphrey VF 24–2 testing (HVF; Carl Zeiss Meditec, Inc., Dublin, CA) was performed for the assessment of VF defects.

The ancillary tests were evaluated separately by 2 of the authors (KS, RA) and the descriptions mentioned in the text were the ones agreed upon by the 2 authors.

Statistical analysis

Statistical analyses were performed using SPSS (version 27.0; IBM Corp., Armonk, NY). Tests for normality of data were first performed using the Kolmogorov–Smirnov and Shapiro–Wilk analysis. Measurements of continuous variables were summarized using means, standard deviation (SD), median and range. Categorical variables were presented as frequencies and percentages. When the data were normally distributed, the comparison between baseline and end of study parameters was performed using Student's *t* test. However, when normal distribution was not achieved, the non-parametric Mann–Whitney test was computed. In order to test the associations between two categorical variables, Fisher's exact test was used. Generalized estimating equations (GEE) were used to adjust for correlations between the eyes regarding ERG parameters, while taking into consideration the age and the time interval between the onset of symptoms to AIR diagnosis. Measurements of the GEE model were summarized using regression coefficients (beta), standard errors (SE), confidence interval (CI), Quasi-likelihood under independence model criterion (QIC), and *p* value. Intraclass correlation coefficients (ICC) between the eyes for VA and ERG parameters at presentation were computed. Kaplan–Meier curve was designed in order to evaluate the rate of visual deterioration throughout the entire study. p value < 0.05 was considered statistically significant.

Results

Demographic features and underlying medical conditions

Nine patients ($n = 6$ males) were included in this study, with a mean ± SD age of 65 ± 13 years at presentation (median 67, range 44–80). Mean duration of follow-up was 63 months (median 63, range 18–120). Patients were followed-up between the years 2009 and 2019.

Five patients ($n = 4$ males) had a previous history of malignancy: three had prostate adenocarcinoma, one had non-small cell lung adenocarcinoma (NSCLC), and one had carcinoma of colon (Table 1). Patient 1 also had previous renal cell carcinoma. Previous malignancy was diagnosed at a mean of 11 years before diagnosis (median 11, range 1–20 years). Only two of these patients were being actively treated for metastatic disease at the time of presentation: patient 4 with bone metastases secondary to prostate cancer was treated with Goserelin (GnRH analogue) and patient 5 with brain metastases secondary to NSCLC was treated with Afatinib (tyrosine kinase inhibitor). Mean age of patients with pAIR at the time of presentation was 70 years (median 68, range 57–80). Patients 1 and 4 deceased 4.5 and 1.5 years after their first presentation, respectively.

In four patients ($n = 2$ males), an extensive work-up did not reveal any underlying malignancy at presentation as well as throughout the period of the follow-up. The mean age

Table 1 Gender, age at presentation, ocular symptoms, interval between first symptom and diagnosis, previous malignancy, interval between previous malignancy and present complaints, family history of malignancy, personal history of autoimmune diseases and treatment

Patient's number	Gender	Age at presentation (years)	Ocular symptoms	Interval between first symptom and diagnosis (months)	Previous malignancy	Interval between previous malignancy and present complaints (years)	Family history of malignancy	Personal history of autoimmune diseases	LogMAR visual acuity at presentation		LogMAR visual acuity (LogMAR) at last follow-up		Treatment
									RE	LE	RE	LE	
#1	M	68	Decreased vision	12	RCC and prostate Ca	20	No	No	0.3	NA	1	NA	A
#2	F	67	Decreased vision, VF defects, Nyctalopia	48	Ca of colon	5	No	No	0	0	0.2	0.7	S, A, C
#3	M	80	Blurred vision, Photophobia	12	Prostate Ca	16	No	No	NA	0.4	NA	0.4	S, A changed later to M
#4	M	57	Decreased vision, Nyctalopia	36	Prostate Ca	1	No	No	1	1.3	1	1.3	No treatment
#5	M	79	Blurred vision, Nyctalopia	12	Lung adenocarcinoma	11	Son had GBM	Hypothyroidism	0.15	0.15	0.2	0.3	S, IVIG
#6	M	47	VF defects	36	No	NA	Son had GBM, two sisters had breast cancer	No	0.15	2	2	2	P, S, A, R
#7	F	65	Decreased vision	60	No	NA	No	Hypothyroidism, fibromyalgia	0.1	0.1	0.15	0.1	P, A
#8	F	44	Decreased vision, Nyctalopia	84	No	NA	Mother and sister had breast cancer	Graves' disease	1.1	0.8	2	0.79	P, A, R
#9	M	75	Blurred vision, Decreased vision	24	No	NA	No	No	0.4	0.4	0.7	0.4	P, A

M male, *F* female, *VF* visual fields, *NA* not applicable, *GBM* glioblastoma multiforme, *RCC* renal cell carcinoma, *Ca* carcinoma, *P* plasmapheresis, *S* systemic steroids, *A* azathioprine, *R* rituximab, *C* cyclosporine, *M* mycophenolate mofetil, *IVIG* intravenous immunoglobulin

of these patients at the time of presentation was 58 years (median 56, range 44–75).

Two patients with (*n*) pAIR and one patient with pAIR had a personal history of autoimmune disease (Table 1). Two patients with (*n*) pAIR and one patient with pAIR had a family history of malignancy: patient 6 with (*n*) pAIR had a son who died at the age of 22 years because of glioblastoma multiforme (GBM) and two of his sisters were diagnosed with breast cancer. The mother and sister of patient 8 suffered from breast cancer. The son of patient 5 died at the age of 48 years because of GBM (Table 1).

Ocular signs and symptoms

Seven patients exhibited bilateral eye involvement (patients 1 and 3 previously underwent retinal detachment repair by pars plana vitrectomy and silicone oil tamponade. We therefore could not attribute the changes of the ERG responses in these eyes exclusively to AIR, and they were excluded from the study, yielding 16 eyes). The most common presenting symptom was reduced visual acuity ($n=6/9$ patients), followed by nyctalopia ($n=4/9$), blurred vision ($n=3/9$), VF defects ($n=2/9$), and photophobia ($n=1/9$; Table 1). The mean time interval between onset of ocular symptoms and diagnosis was 36 months (range 12–84, median 36).

Mean LogMAR VA at presentation and at last follow-up was 0.72 ± 0.9 and 1.1 ± 1.2, respectively ($p=0.17$). At presentation, there was good VA in 8/16 eyes (50%), and moderate or severe visual loss in 4/16 eyes each (25%). At the last follow-up, good VA and moderate visual loss was observed in 5/16 eyes each (31%) and severe visual loss was observed in 6/16 eyes (38%). Kaplan–Meier survival curve (Fig. 1) shows the cumulative incidence of vision deterioration by at least one line on the Snellen chart during the entire study. Half of the eyes that exhibited visual deterioration experienced it up to 70 months from presentation.

Ocular examination demonstrated no signs of anterior chamber or vitreous inflammation. Apart from patient 6 who had a normal fundus examination at presentation and all throughout follow-up (Fig. 2), all other patients exhibited some form of posterior segment pathology (Table 2). The two most commonly encountered ocular signs were optic disc atrophy (OA) and bone spicule-like pigmentation; each observed in 56% of the eyes (9/16 eyes). Additional frequent signs included retinal arteriolar attenuation and retinal atrophy, each observed in 50% of the eyes ($n=8/16$ eyes) as well as cystoid macular edema (CME), which was observed in 25% of the eyes ($n=4/16$ eyes). OA was more prevalent in the eyes with pAIR than eyes with (*n*) pAIR ($p=0.04$) (Table 2).

Ancillary tests

The most frequent VF defects were tunnel vision and central/paracentral scotomas; each observed in 25% of eyes ($n=4/16$ eyes). Arcuate scotoma was observed in 19% of eyes ($n=3/16$ eyes), and diffuse VF defects were observed in 13% of eyes ($n=2/16$ eyes). VFs were interpreted as normal in 19% of the eyes (3/16) (Table 3).

OCT was interpreted as normal in 50% of the eyes ($n=8/16$ eyes) (Tables 3, 4). The most frequent abnormality seen in half of the eyes ($n=8/16$ eyes) was attenuation of the nerve fiber layer. Attenuated outer nuclear layer and disrupted/absent EZ was each observed in 38% of the eyes

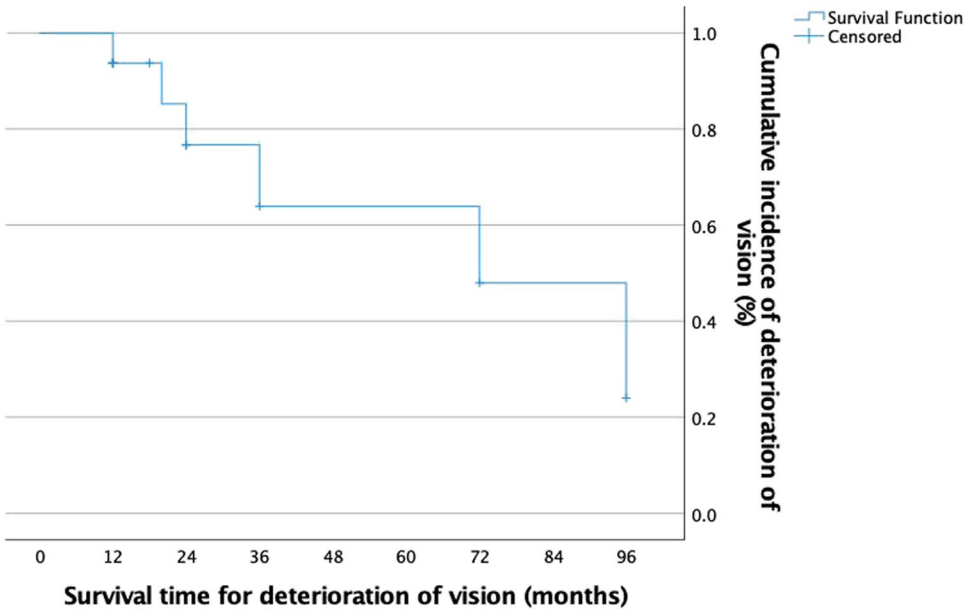

Fig. 1 Kaplan–Meier survival curve shows the cumulative incidence of vision deterioration by at least one line on the Snellen chart during the entire study. Half of the eyes that exhibited visual deterioration experienced it up to 70 months from presentation

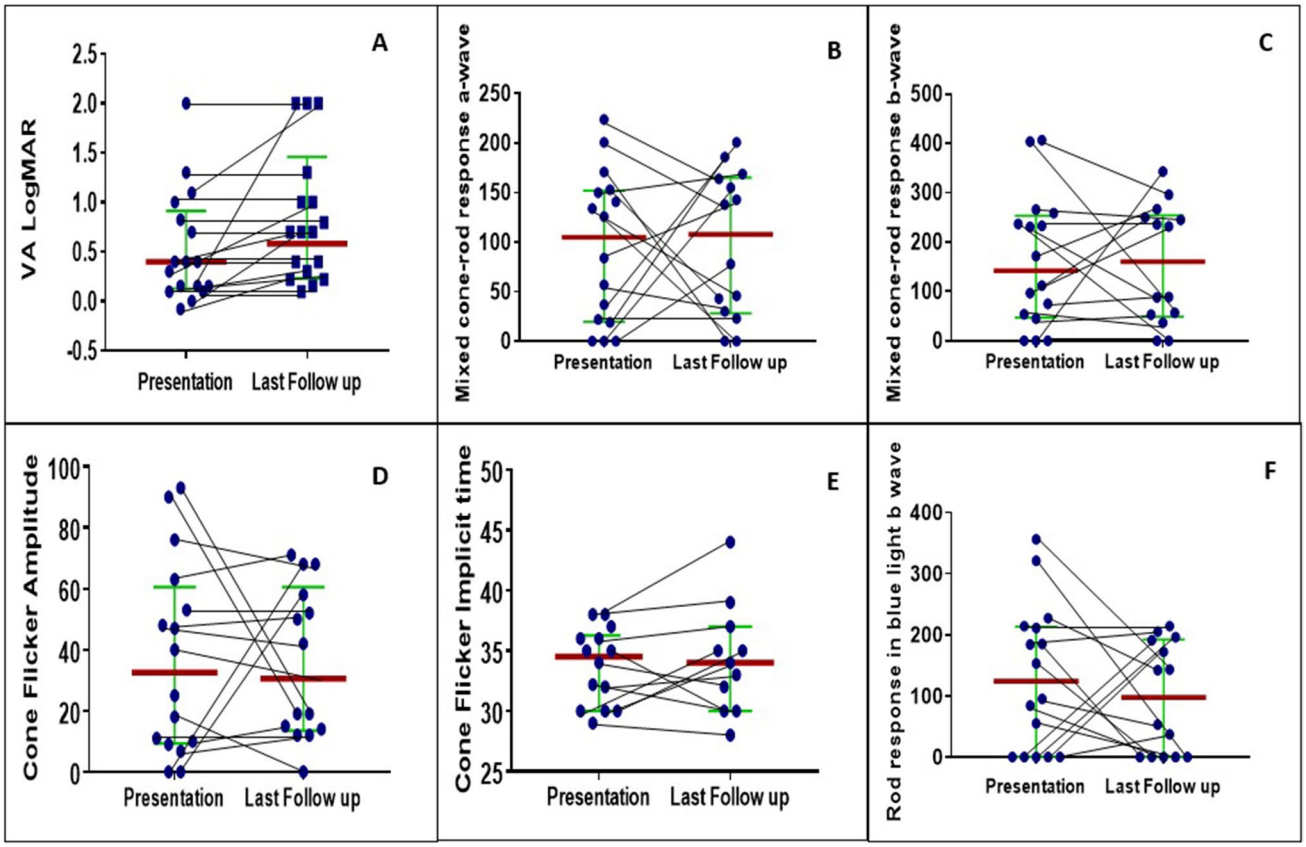

Fig. 2 Visual acuity and electroretinography parameters at the initial visit and the most recent visit in patients with autoimmune retinopathy. **A** LogMAR visual acuity. **B** Mixed rod-cone response a-wave amplitude. **C** Mixed rod-cone response b-wave amplitude. **D** 30-Hz flicker amplitude. **E** 30-Hz flicker implicit time. **F** Scotopic rod response b-wave amplitude. The lower and upper lines show the 25th–75th percentile. The middle line represents the median. Vertical line extends from the minimum to the maximum. Separate dots show far out values.

($n=6/16$ eyes). CME was observed in 25% of the eyes ($n=4/16$ eyes).

FA was interpreted as normal in nine eyes. Two eyes demonstrated a mixed pattern of hypo-fluorescence and hyper-fluorescence and two eyes exhibited macular capillary leakage compatible with CME. FA was not available for three eyes (patients 1 and 9; Table 3). Overall, four patients had abnormalities in VF, FA, and OCT tests. Three patients had normal OCT but defective VF whereas in two patients, no abnormality was detected in either FA, VF, or OCT (Table 3).

The most commonly encountered serum ARA was anti-α-enolase antibody (46 kDa; $n=4$ patients) identified only in (*n*) pAIR patients (Table 3). In two patients, anti-carbonic anhydrase II antibodies (30 kDa) were detected. Other serum antibodies detected were targeted against proteins at the molecular weights of 80 kDa, 70 kDa, 50 kDa, 40 kDa, 38 kDa, 36 kDa, 33 kDa, 31 kDa, 30 kDa, and 29 kDa. Five patients, four of whom were diagnosed as pAIR, had a

Table 2 Ocular signs at presentation in the eyes with paraneoplastic retinopathy and in the eyes with non-paraneoplastic retinopathy

Fundus examination (eyes)	All 16 eyes	Paraneoplastic retinopathy (8 eyes)	Non-paraneoplastic retinopathy (8 eyes)	*p* value
Normal	2 (12.5%)	0	2 (25%)	0.5
Optic disc pallor	9 (56%)	7 (88%)	2 (25%)	0.04
Bone spicule-like pigmentation	9 (56%)	5 (63%)	4 (50%)	0.9
Retinal arteriolar attenuation	8 (50%)	5 (63%)	3 (38%)	0.6
Retinal atrophy	8 (50%)	6 (75%)	2 (25%)	0.06

Table 3 Optical coherence tomographic features, fluorescein angiographic features, visual field findings, and serum anti-retinal antibodies

Patient's number	Optical coherence tomography		Fluorescein angiography		Visual fields		Serum anti-retinal antibodies
	RE	LE	RE	LE	RE	LE	
#1	NL	NR	NA	NR	Tunnel vision	NR	36 kDa
#2	Attenuated ONL, absent or disrupted EZ, attenuated NFL, CME	Attenuated ONL, absent or disrupted EZ, attenuated NFL, CME	Macular capillary leakage	Macular capillary leakage	Arcuate scotoma	Tunnel vision	50 kDa
#3	NR	NL	NR	NL	NR	NL	(50 kDa) (anti-pigment epithelium derived factor Ab)
#4	Attenuated ONL, absent or disrupted EZ, attenuated NFL	Attenuated ONL, absent or disrupted EZ, attenuated NFL	Mixed pattern of hyper- and hypo-fluorescence	Mixed pattern of hyper- and hypo-fluorescence	Paracentral scotoma	Paracentral scotoma	NA
#5	Attenuated NFL	Attenuated NFL	NL	NL	Diffuse VF defect	Diffuse VF defect	30 kDa (anti-carbonic anhydrase II Ab)
#6	NL	NL	NL	NL	Central scotoma	Central scotoma	46 kDa (anti-α-Enolase Ab)
#7	NL	NL	NL	NL	NL	NL	46 kDa (anti-α-Enolase Ab), 40 kDa, 70 kDa
#8	NL	NL	NL	NL	Arcuate scotoma	Arcuate scotoma	46 kDa (anti-α-Enolase Ab), 31 kDa, 80 kDa
#9	Attenuated ONL, absent or disrupted EZ, attenuated NFL, CME	Attenuated ONL, absent or disrupted EZ, attenuated NFL, CME	NA	NA	Tunnel vision	Tunnel vision	46 kDa (anti-α-Enolase Ab), 30 kDa (anti-carbonic anhydrase II Ab), 29 kDa, 31 kDa, 33 kDa, 38 kDa

NL normal, *NA* not applicable, *NR* not relevant, *NFL* nerve fiber layer, *ONL* outer nuclear layer, *EZ* ellipsoid zone, *VF* visual field, *Ab* antibody

Table 4 Optical coherence tomographic features at presentation in the eyes with paraneoplastic retinopathy and in the eyes with non-paraneoplastic retinopathy

Optical coherence tomographic features	All 16 eyes	Paraneoplastic retinopathy (8 eyes)	Non-paraneoplastic retinopathy (8 eyes)	*p* value
Normal	8 (50%)	2 (25%)	6 (75%)	0.14
Attenuated nerve fiber layer	8 (50%)	6 (75%)	2 (25%)	0.14
Attenuated outer nuclear layer	6 (38%)	4 (50%)	2 (25%)	0.6
Absent or disrupted ellipsoid zone	6 (38%)	4 (50%)	2 (25%)	0.6
Cystoid macular edema	4 (25%)	2 (25%)	2 (25%)	0.9

Table 5 Electroretinogram parameters at presentation and after therapy including cone flicker amplitudes and implicit time, mixed cone-rod a- and b-waves and rod b-wave response in blue light. *NL* normal limit, *NR* non-recordable, *RE** RE at presentation, *RE*** RE after therapy, *LE** LE at presentation, *LE*** LE after therapy; *in patient #4, the ERG was done only once. *W* worse, *I* improved, *S* stable. Parameters that have worsened in accordance with the definitions in the methods section are red-colored while parameters that improved are green-colored. Stable parameters are not color-coded

ERG Parameters	Cone Flicker Amplitude (NL ≥60uV)				Cone flicker implicit (NL up to 33msec)				Mixed rod-cone response a-wave amplitude (NL ≥100uV)				Mixed rod-cone response b-wave amplitude (NL ≥400uV)				Rod b-wave response in blue light (NL ≥200uV)				Change in ERG Test	
Patient's Number-Time of follow-up ERG	RE*	RE**	LE*	LE**	RE*	RE**	LE*	LE**	RE*	RE**	LE*	LE**	RE*	RE**	LE*	LE**	RE*	RE**	LE*	LE**	RE	LE
#1-4y	63	71			32.2	30			84	143			259	250			214	214			S	
#2-1y	11	12	10	12	36	37	38	39	22	23	37	46	112	53	54	37	95	53	55	37	S	S
#3-4y			18	15			30	35			150	201			75	89			NR	NR		S
#4*	NR		NR		NR		NR		19		NR		45		NR		NR		NR			
#5-1.5y	76	58	53	68	30	34	30	35	153	78	57	169	266	245	97	343	184	172	84	191	S	I
#6-10y	93	68	90	52	35	39	36	37	201	186	224	155	407	296	404	232	321	205	356	196	W	W
#7-3y	48	19	47	19	35	30	34	33	171	43	126	30	231	88	172	57	227	NR	185	NR	W	W
#8-1.5y	40	42	25	50	29	28	29	33	134	138	141	164	233	236	237	267	153	142	211	143	S	S
#9-1y	6.8	14	9	NR	38	44	37	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	S	S

single ARA. Three patients, all diagnosed as (*n*) pAIR, had multiple bands of ARA (≥3 bands). One patient (patient 4) declined testing for serum ARA (Table 3).

ERGs were available for nine patients and 16 eyes (as mentioned above). ERG parameters were obtained from the first ERG recorded at presentation before initiating therapy as well as from the last available ERG test performed at a mean of 3.3 years after presentation (median 2.3, range = 1–10 years).

Mean cone flicker amplitude was 36.8 initially (normal ≥ 60 µV) vs. 35.7 on last exam (Table 5, Fig. 2). Mean cone flicker implicit time at presentation was 33.5 ms (normal ≤ 33 ms) vs. 34.9 ms on last exam. Mean a–wave amplitude of the dark adapted mixed rod-cone response at presentation was 94.9 (normal ≥ 100 µV) vs. 98.3 on last exam. Mean b–wave amplitude of the dark-adapted mixed rod-cone response at presentation was 162 (normal ≥ 400 µV) vs. 156.6 on last exam. Mean b-wave amplitude of the dark-adapted rod response employing dim blue light was 130.3 (normal ≥ 200 µV) at presentation vs. 96.6 on last exam. No significant difference was observed between the initial and most recent exam in the mean values of all of the above ERG parameters, also after excluding the non-measurable responses. ICC at presentation was 0.97 for cone flicker amplitude, 0.97 for cone flicker implicit time, 0.85 for a–wave amplitude of the mixed rod-cone response, 0.91 for the b–wave amplitude of the mixed rod-cone response, 0.89 for the b-wave amplitude of the dark-adapted rod response, and 0.81 for VA. GEE showed that for cone flicker amplitude, beta ± SE was 0.4 ± 0.09 (confidence interval (CI) 12–53, QIC 3973, $p = 0.01$), for cone flicker implicit time, beta ± SE was 0.34 ± 0.02, (CI 30–38, QIC 293, $p = 0.01$)), for mixed rod-cone response a-wave amplitude, beta ± SE was 1.01 ± 0.03 (CI 55–166, QIC 20,332, $p = 0.01$), for mixed rod-cone response b-wave amplitude, beta ± SE was 1.12 ± 0.27 (CI 53–266, QIC 18,880, $p = 0.01$), and for rod

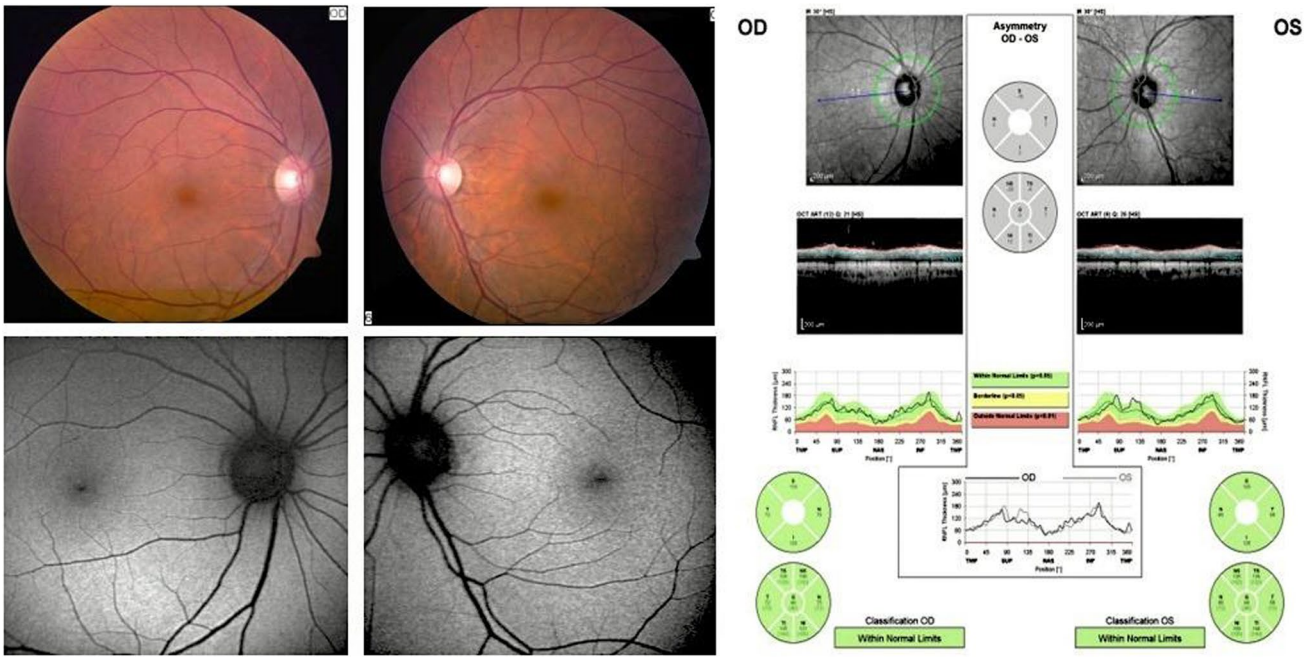

Fig. 3 In the left panel, normal color fundus photographs and short-wave autofluorescence images are seen. In the right panel, normal nerve fiber layer thickness is demonstrated in both eyes by optical coherence tomography

b-wave response in blue light, beta ± SE was 1.41 ± 0.31 (CI 106–208, QIC 16,344, $p = 0.01$).

Worsening of ERG tests over time was observed in 4/14 eyes (28.6%), stability was seen in 9/14 eyes (64.3%), and improvement in 1/14 eye (7.1%) (In patient #4, the ERG was done only at presentation; therefore, the total number of eyes analyzed for assessing ERG changes over time was 14) (Table 5).

Management

Eight patients received IMT with or without plasmapheresis while one patient declined treatment. Seven patients were managed by more than one form of therapy and one patient received azathioprine monotherapy (Table 1).

The following are two representative case descriptions of a patient with (*n*) pAIR and a patient with pAIR:

Case report 6

A 47-year-old healthy man presented with a 3-year history of bilateral visual disturbances. He described "bagel-shaped" blurriness of vision around fixation that initially started in the left eye and after a period of 18 months affected the right eye as well. On examination, LogMAR VA was 0 in each eye, with normal intraocular pressures, anterior segments, and funduscopy (Fig. 3). Fundus autofluorescence, FA, and OCT did not exhibit any pathological findings (Fig. 3, 6). However, serial VF tests demonstrated bilateral enlarging central scotomata (Fig. 4). Brain MRI, cerebrospinal fluid examination, and total body CT scans were normal. Electrophysiological studies that included FF-ERG, visual evoked potential and electro-oculograms were also within normal limits (Fig. 5, 6). Multifocal ERG testing revealed subnormal amplitudes and increased latency bilaterally in the central 10 degrees and a progressive reduction in amplitudes over 3 years of follow-up. Testing for serum ARA revealed the presence of anti-α- enolase autoantibodies. The patient was thus diagnosed as (*n*) pAIR. Treatment was initiated with intravenous methylprednisolone (1 g/day for 3 consecutive days) followed by a tapering regimen of oral steroids. Subsequently, azathioprine was added as a steroid-sparing agent and the patient underwent plasmapheresis over a 3-week period. No subjective or objective improvement was noted and there was no change in the titer of anti-α-enolase autoantibodies in the post-treatment period in comparison to the pre-treatment titer. Because of progressive worsening in multifocal ERG parameters and because of enlarging central scotomata, rituximab therapy was instituted. Again, no improvement was demonstrated by ancillary testing. Notably, the patient's 22-year-old son passed away because of GBM and 2 of his sisters were diagnosed with breast cancer. After a follow-up period of 10 years, no malignancy was

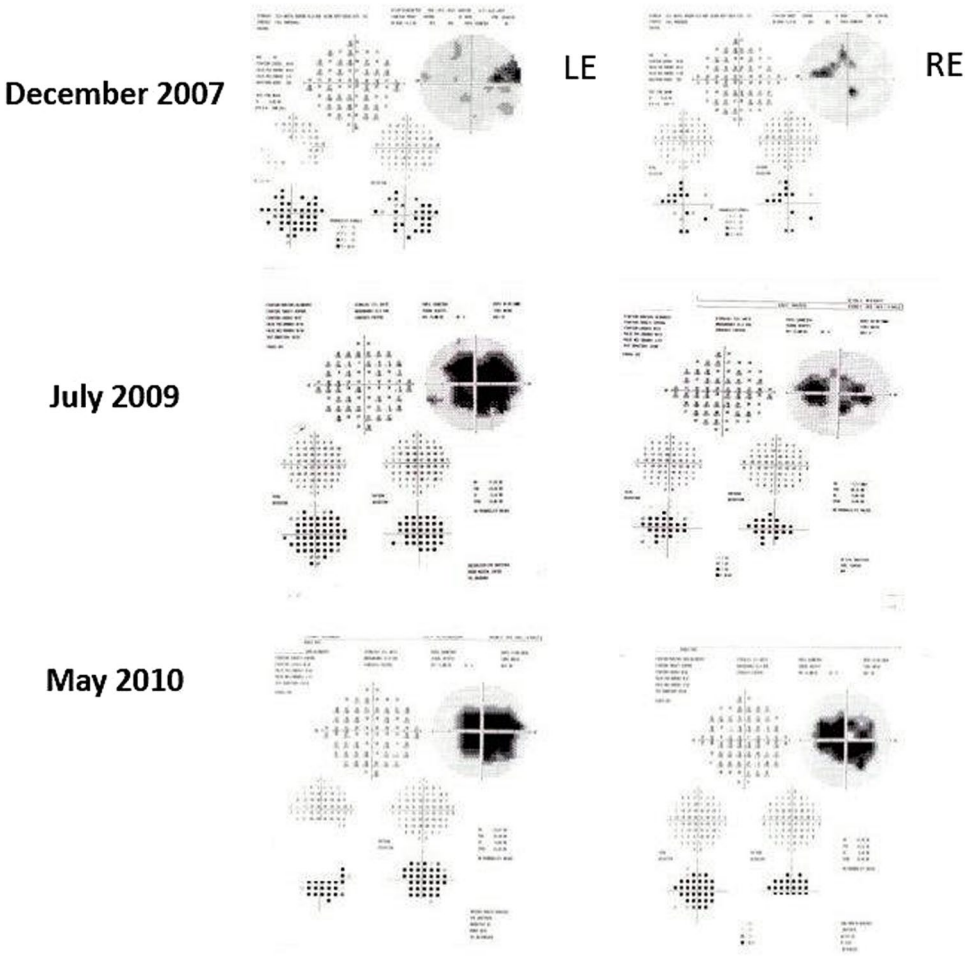

Fig. 4 Central visual fields (10–2) over a 3-year-period of follow-up demonstrate progressively enlarging central scotomata in both eyes

detected on repeated examinations. LogMAR VA was 2 in each eye. On 2 instances, the patient complained of peripheral scotomata while on azathioprine monotherapy which were recorded by VF testing and were completely reversible on re-institution of prednisone therapy (Fig. 7).

Case report 2

A 67-year-old female patient presented because of progressive visual disturbances and nyctalopia over the preceding 4 years. The patient noted bumping into things and has fractured her arm on a trip. Past medical history revealed colonic adenocarcinoma, which was resected by right hemicolectomy 4 years earlier and was subsequently treated by chemotherapy. LogMAR VA was 0 in each eye with normal intraocular pressures. Anterior segments and vitreous were quiet with bilateral pseudophakia. Funduscopy (Fig. 8) revealed bilateral OA, diffuse retinal atrophy, markedly attenuated retinal vessels with lack of retinal vasculature in the periphery and minimal fine bone spicule-like pigmentation. VF testing revealed an inferior arcuate defect in the right eye and peripheral constriction of the VF in the left eye (Fig. 9). OCT demonstrated atrophy of outer nuclear layers and disrupted outer retinal bands that were more extensive in the left than in the right eye (Fig. 10). In addition, extensive nerve fiber layer thinning was noted bilaterally. FF-ERG revealed significantly reduced a- and b-wave amplitudes. Electro-oculographic testing exhibited severely reduced Arden ratios of 109% in the RE and 108% in the LE (normal 185–250%). Family history did not reveal a suspicion for a genetic form of retinal degeneration. Serum was tested for ARA and was positive for autoantibodies against a retinal antigen of 50kD. The patient was initially treated with a 3-day pulse therapy of intravenous methylprednisolone (1000 mg/day) followed by an oral steroid taper. Azathioprine and cyclosporine were added later during the course of treatment. After a 4-year follow-up period, the patient maintained a near visual acuity of Jaeger 2 in the right eye and Jaeger 7 in the left eye.

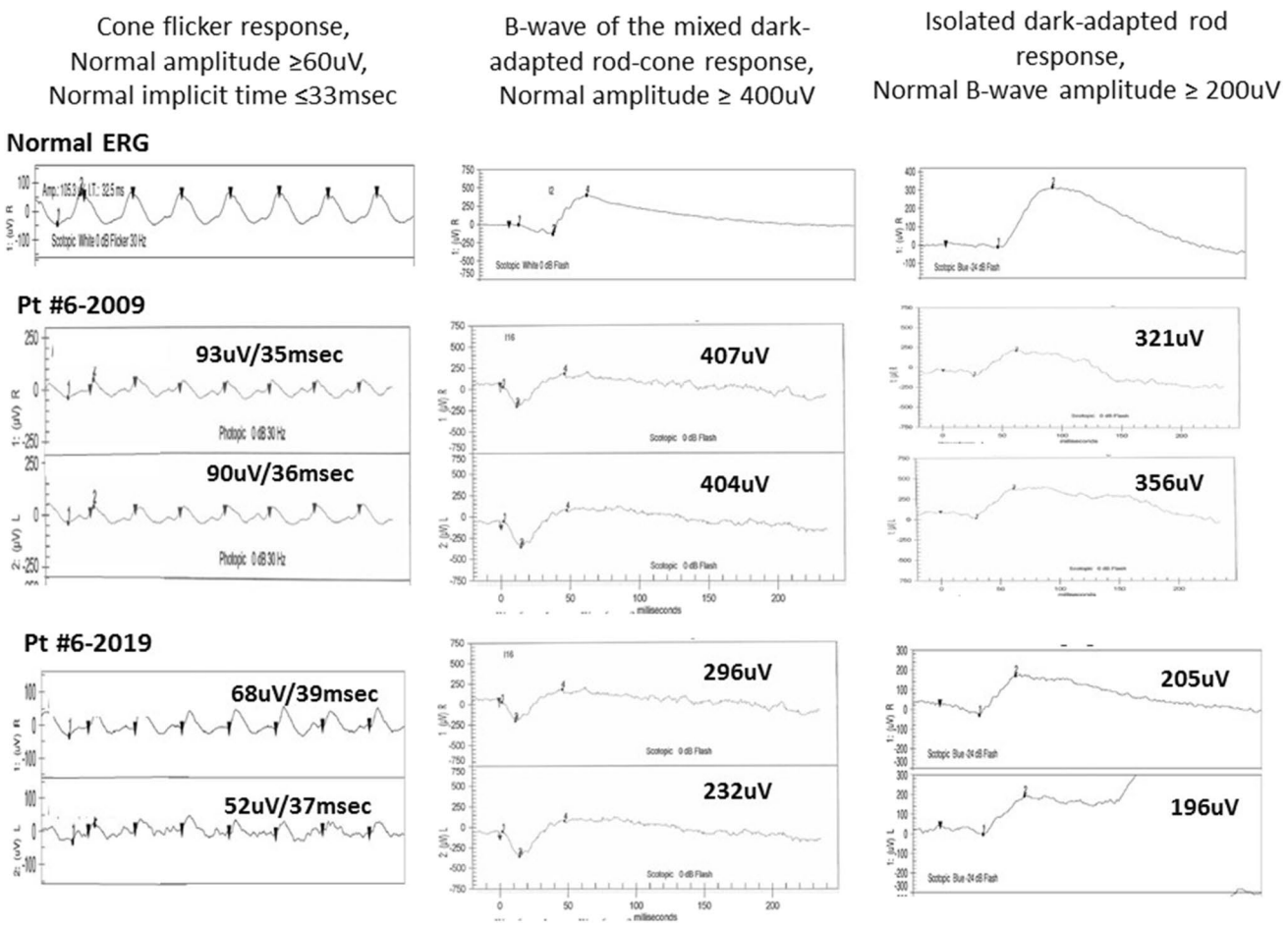

Fig. 5 In the upper panel, normal responses of the cone flicker, of the b-wave of the mixed dark-adapted rod-cone response, and of the b-wave of the isolated rod response are demonstrated. In the middle and lower panels, ERG responses are shown (at presentation and 10 years later)

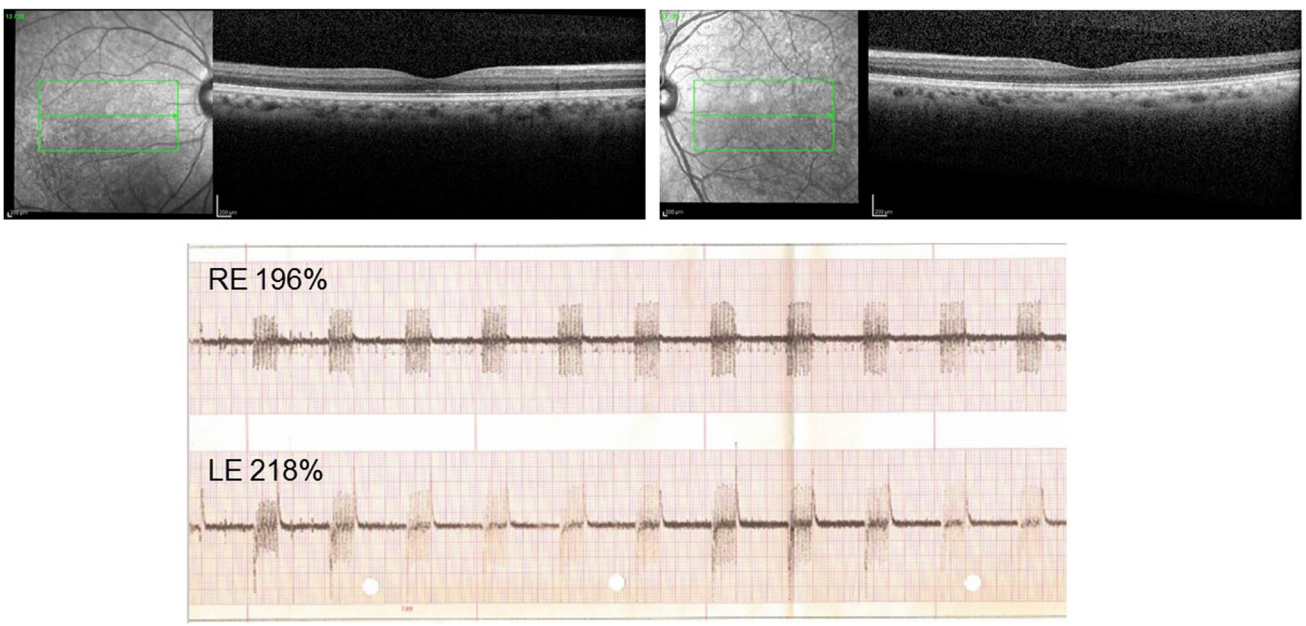

Fig. 6 In the upper panel, normal foveal contour is demonstrated in both eyes by optical coherence tomography. In the lower panel, EOG responses at presentation are shown (Arden ratio in the right eye was 196% and in the left eye was 218%)

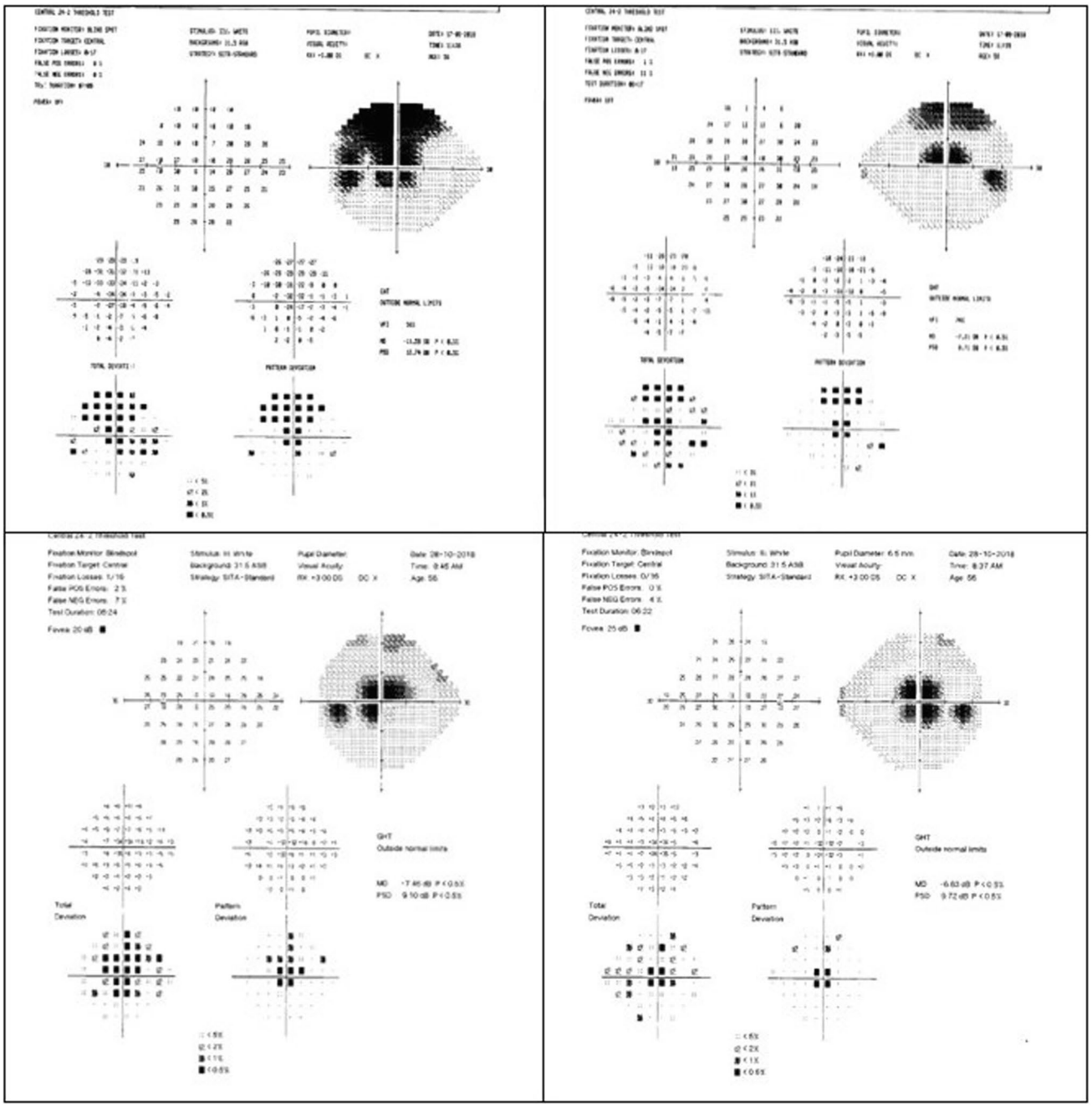

Fig. 7 The patient presented with complaints of darkness in the upper part of the left visual field 3 weeks after discontinuing prednisone while being maintained on azathioprine monotherapy. SITA standard visual field (24–2) revealed new superior scotomata in both eyes, bigger and connected to the pre-existing central scotoma in the left eye. Treatment with prednisone was instituted (1 mg/kg/day for 2 weeks) followed by a tapering regimen. Five weeks later, resolution of the superior scotomata was noted in both eyes, while the central scotomata persisted

Discussion

This study highlights the importance of maintaining a high index of suspicion of AIR, particularly in late middle-aged and elderly patients with "unexplained" visual loss, in light of the non-specific posterior segment signs and the inconsistency of the routinely used ancillary tests.

Firstly, lack of agreement between the commonly used tests, namely, OCT and VF, was observed in one-third of patients who exhibited normal OCTs while having abnormal VFs. In two patients (22%), the symptoms of visual

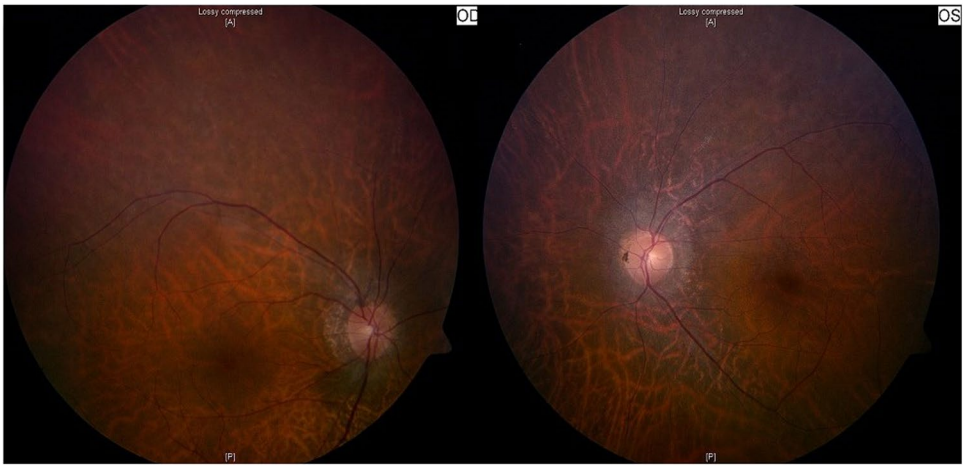

Fig. 8 Color fundus photographs showing markedly attenuated retinal vessels with absence of retinal vasculature in the upper retina of the right eye. Diffuse retinal atrophy is noted with a small area of pigmentation on the nasal side of left optic disc

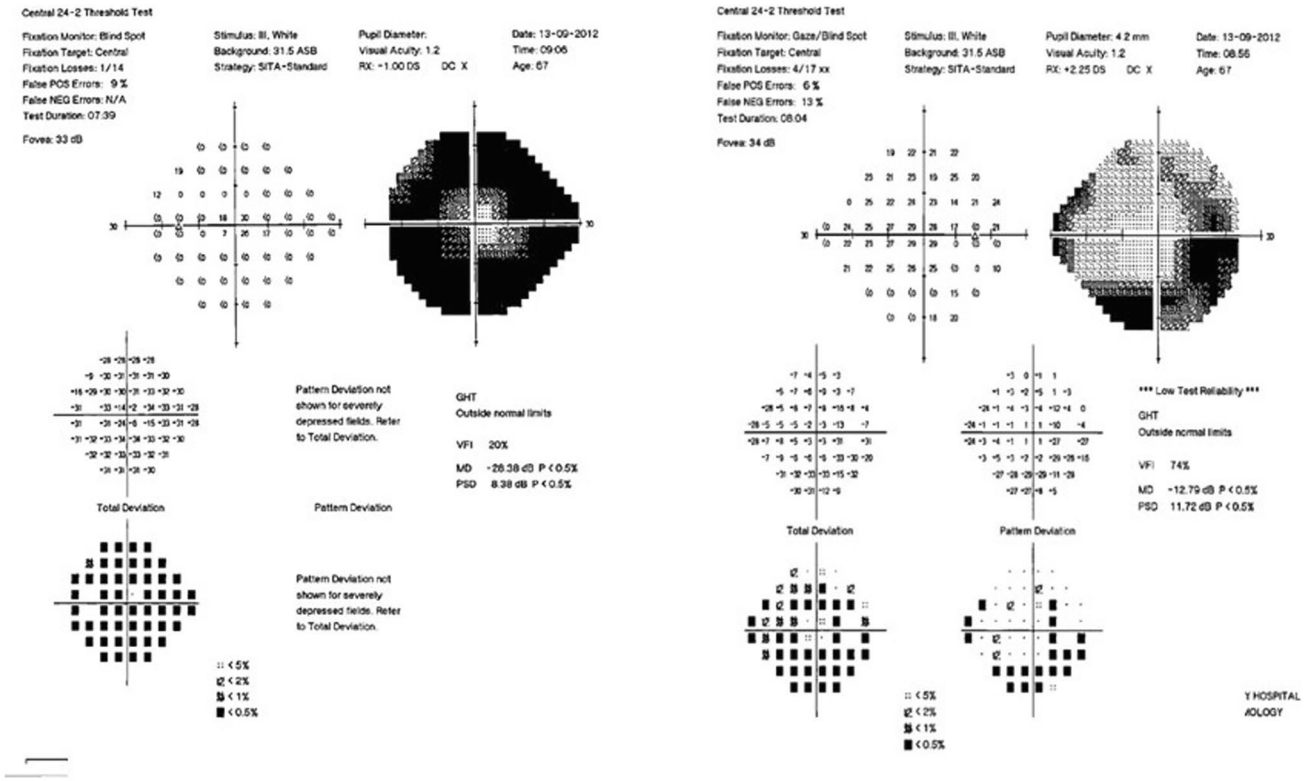

Fig. 9 SITA standard (24–2) visual fields demonstrate an inferior arcuate scotoma in the right eye and tunnel vision (central island) in the left eye

disturbances were not reflected in either OCT, VF, or FA. However, four patients (44%) demonstrated abnormalities on all three of the above tests. The challenge in diagnosing this entity was reflected in the markedly long mean interval of 3 years between the onset of ocular symptoms and diagnosis.

Secondly, electrophysiological testing helped in triggering the workup of the patients' complaints, since it demonstrated reduced parameters in most of patients. This study confirms previous ones that showed that ERG was a sensitive test in revealing the underlying retinal dysfunction and in serving as a functional correlate to assess for disease progression and response to treatment[20]. Good inter-ocular symmetry for VA and ERG parameters at presentation was illustrated by ICC. GEE demonstrated correlation between the fellow eyes for all ERG parameters between baseline and last exam. Correlation was higher for mixed rod-cone response a- and b-wave amplitudes and for rod b-wave

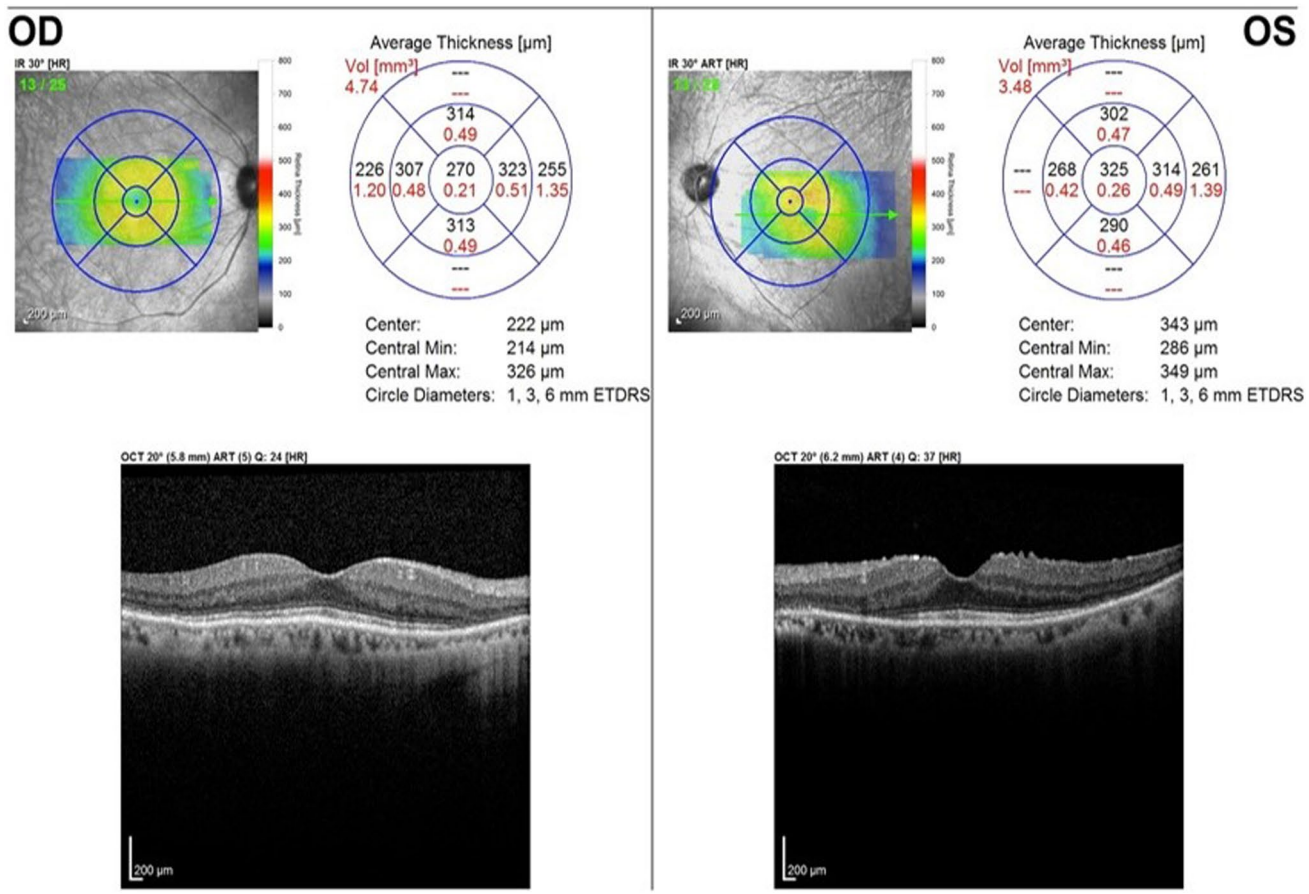

Fig. 10 Optical coherence tomography demonstrates attenuated outer nuclear layers and outer retinal bands in both eyes with preservation of the very central part of the ellipsoid zone, more in the right than in the left eye

response in blue light than for cone flicker amplitude and implicit time.

In the present study, five patients had pAIR induced by prostate, lung, and colon malignancies. Previous malignancy was diagnosed on average 11 years prior to the patients' presentation. Careful history taking in patients with unexplained visual loss is the cornerstone in establishing the diagnosis of pAIR. Patients whose malignancy has completely resolved many years earlier may not be aware of the possible link between the previous cancer and the present visual complaints; they may therefore not disclose their full past medical history on presentation. In the first report published in 1976 on pAIR, Sawyer et al. [17] reported on three patients who developed photoreceptor degeneration 1 to 4 months preceding or following the discovery of an anaplastic tumor. Subsequent reports described longer intervals between the preceding malignancy and the onset of the visual disturbances. Igarashi N et al. [24] reported pAIR developing 10 years after complete remission from breast cancer.

Four of our patients had (*n*) pAIR; they had no history of malignancy and extensive systemic work-up at the time of their presentation did not reveal an occult underlying malignancy; it was also not revealed over the median follow-up period of 5 years. Ultimately, (*n*) pAIR is a diagnosis of exclusion and diligent regular screening at regular intervals is essential for tumor surveillance.

Patients with (*n*) pAIR were younger than patients with pAIR (median was 56 vs 68 years respectively). Similarly, Maleki et al. [20] and Finn et al. [11] reported on a median age of 49 and 59 years in patients with (*n*) pAIR, respectively, while Makiyama et al. [25] reported on a median of 66 years in patients with pAIR.

Optic disc atrophy and bone spicule-like pigmentation were the two most commonly encountered ocular signs. OA was more prevalent in the eyes with pAIR than the eyes with (*n*) pAIR. Weleber et al. [8] reported on the clinical and electrophysiological features in 12 patients with anti-enolase retinopathy; seven of them developed optic disc pallor, presumably from attrition of ganglion cells (4 patients had (*n*) pAIR and 3 had pAIR). Meticulous assessment of the sectorial thickness of each retinal layer at macular level will enable us to better define the pathological retinal layers.

The most commonly detected ARA in our study was anti-α-enolase antibody. It was detected in 4 patients (44%); all of whom were diagnosed as having (*n*) pAIR. Anti-recoverin antibodies were not detected in our cohort. Weleber et al. [8] reported that among 37 patients diagnosed with AIR at Portland, Oregon, anti-α-enolase antibody was the most commonly detected autoantibody (12 patients (32%)) and most of the patients affected by anti-enolase retinopathy were confirmed to be (*n*) pAIR. Anti-α-enolase antibodies have also been detected in healthy individuals [26, 27] and in patients with autoimmune diseases [27, 28]. This could be related to the multifunctional properties of α-enolase; as besides its glycolytic function, it has also been demonstrated to function as a structural protein, a stress protein induced by hypoxia, a controller of cell growth and differentiation, a regulator of *c-myc* protooncogene expression, and possibly a suppressive lymphokine[28].

Anti-enolase retinopathy almost invariably begins with central visual dysfunction but is characterized by more protean clinical features than anti-recoverin retinopathy. Each of the four affected patients in our cohort found positive for the presence of anti-enolase presented with a different VF defect: arcuate and central scotomata, tunnel VF, and normal VF. Weleber et al. [8] described gradual visual impairment to be a characteristic feature of anti-enolase retinopathy and reported that visual loss rarely becomes as profound as with anti-recoverin retinopathy, often remaining relatively stable for years. However, in our cohort, 2 patients with anti-enolase retinopathy exhibited an extinct ERG (patient 9 at presentation and patient 7 over the course of follow-up). Although it is unclear whether the additionally detected autoantibodies had pathologic significance, their existence apparently contributed to the diverse clinical, electrophysiological, and perimetric phenotypes.

The second most commonly encountered auto-antibody was anti–carbonic anhydrase II (anti-CAII, 30 kDa), which was detected in 2 patients. It had also been detected in several autoimmune conditions, such as systemic lupus erythematosus, Sjögren's syndrome, autoimmune cholangitis, chronic pancreatitis, endometriosis, systemic sclerosis, and type I diabetes as well as in healthy individuals [29]. Adamus et al. [30] reported that anti-CAII autoantibodies revealed affinity to different epitopes, depending on whether they originated in patients with or without cancer. In addition, the antibodies targeted different determinants within the molecule during the development of retinopathy from non-paraneoplastic to paraneoplastic, suggesting an intramolecular epitope spreading phenomenon.

OCT was interpreted as normal in 50% of the study eyes. Normal OCT findings were more frequently observed in (*n*) pAIR than in pAIR eyes; however, this did not reach statistical significance. Finn et al. [11] found that retinal disease in AIR eyes with CME was more severe and more aggressive when compared to eyes without CME, as manifested by decreased a- and b-wave amplitudes on FF-ERG. These results are consistent with our study, as the four eyes with CME had extinct ERG at presentation combined with an abnormal funduscopic examination, markedly abnormal OCT and VF defects.

Mantel et al. [31] reported the electrophysiological characteristics of 16 AIR patients with retinal dysfunction and normal fundus appearance. These tests were reported at a single time point, and there was no description of treatment. None of the patients exhibited night blindness. Electrophysiology indicated predominant cone-system dysfunction, either macular or generalized, and 44% had some degree of rod dysfunction. Serum ARA reacted with the retinal proteins of molecular weight between 28.9 and 49.1 kDa, none of those being anti-enolase autoantibodies.

While long-term IMT is considered the mainstay of treatment for AIR, no definitive therapeutic protocol has been established to date [6]. In the present study, patients exhibited mostly stability of the ERG parameters with IMT over the follow-up period. Patient 7 deteriorated rapidly to non-detectable ERG; however, the patient stopped the medication without consulting the treating physician. Better understanding of the underlying immune-mediated processes of AIR will allow the development of effective targeted therapies aiming to arrest disease progression and/or to stabilize and perhaps even improve visual function.

Ferreyra et al. [6] reported on the largest case series of 30 patients with AIR in which the effect of treatment was evaluated. Twenty-nine patients received at least one systemic immunosuppressive medication during treatment (1 patient with CAR received subtenon methylprednisolone acetate at multiple visits during 2 years). Median follow-up was 17 months. The response to treatment was 70% (21 of 30); it consisted of improvement in VA in 5 of 21 patients (24%) and expansion of the VF area of at least 25% in 15 of 21 patients (71%). ERG was not examined routinely; however, two patients showed significant improvement in the ERG. The authors concluded that most AIR patients needed immunosuppression therapy for extended periods and that patients with earlier disease were more responsive than were severely affected patients.

Maleki et al. [20] reported on the efficacy of rituximab as a monotherapy or in combination therapy in six patients with AIR. Stabilization and/or improvement was observed in a high number of patients (75%); this consisted of VA stabilization in eight (66.7%) eyes, VF stabilization in six (50%) eyes and improvement in two (16.7%) eyes and ERG stabilization or improvement in eight (66.7%) eyes.

There are several limitations to this study. It is a retrospective study and includes a small number of patients with heterogeneous ARA profiles and varied treatment regimens

and follow-up periods. Absence of case number rationale was a limitation to statistical tests. In addition, we were dependent on a commercially available laboratory for ARA testing, and antibody titers were not included in the reports. An additional limitation is that the findings of EOG and MF-ERG were not analyzed since they were performed in only a minority of patients. Since FF-ERG stimulates and records responses from the whole retina, macular abnormalities may be missed. Multifocal ERG is an invaluable tool for the detection of macular pathology and is a useful adjunct in the subgroup of patients in which changes to macular architecture are demonstrated by OCT or changes in the VF 24–2 are observed. Nevertheless, this article describes a rare cohort study of patients with (*n*) pAIR and pAIR with prolonged follow-up, treated with long-term multiple IMT demonstrating either stability or worsening as monitored by repeated FF- ERG testing.

In conclusion, AIR is a diagnostic and therapeutic challenge to ophthalmologists. The possibility of presentation with a normal clinical exam and many ancillary tests in some patients contributes to the challenge of establishing the diagnosis. Recognition of this entity requires an integration of clinical intuition, examination findings, and combining the results from multiple ancillary tests. ERG was demonstrated to be a useful marker for assessing disease progression and response to treatment.

Author contribution KS was involved in the design and conduct of the study, collection and analyzing of the data, and writing the manuscript. RA was involved in the management of the clinical cases, the design and conduct of the study, and writing the manuscript. IC, EB, BR, and LT were involved in analyzing the ERG tests and reviewing the manuscript.

Data availability The corresponding author has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (HMO-Hadassah Medical Organization IRB approved the study) and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declarations

Informed consent This type of study does not require an informed consent.

Conflict of interest The authors declare no competing interests.

References

1. Adamus G, Ren G, Weleber RG (2004) Autoantibodies against retinal proteins in paraneoplastic and autoimmune retinopathy. BMC Ophthalmol 4:1–9. https://doi.org/10.1186/1471-2415-4-5
2. Adamus G (2003) Autoantibody-induced apoptosis as a possible mechanism of autoimmune retinopathy. Autoimmun Rev 2:63–68
3. Adamus G, Champaigne R, Yang S (2020) Occurrence of major anti-retinal autoantibodies associated with paraneoplastic autoimmune retinopathy. Clin Immunol 210.https://doi.org/10.1016/j.clim.2019.108317
4. Heckenlively JR, Ferreyra HA (2008) Autoimmune retinopathy: a review and summary. Semin Immunopathol 30:127–134
5. Grange L, Dalal M, Nussenblatt RB, Sen HN (2014) Autoimmune retinopathy. Am J Ophthalmol 157:266. https://doi.org/10.1016/j.ajo.2013.09.019
6. Ferreyra HA, Jayasundera T, Khan NW et al (2009) Management of autoimmune retinopathies with immunosuppression. Arch Ophthalmol 127:390–397. https://doi.org/10.1001/archophthalmol.2009.24
7. Jacobson DM, Thirkill CE, Tipping SJ (1990) A clinical triad to diagnose paraneoplastic retinopathy. Ann Neurol 28:162–167. https://doi.org/10.1002/ana.410280208
8. Weleber RG, Watzke RC, Shults WT et al (2005) Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. Am J Ophthalmol 139:780–794. https://doi.org/10.1016/j.ajo.2004.12.104
9. Chan JW (2003) Paraneoplastic retinopathies and optic neuropathies. Surv Ophthalmol 48:12–38
10. Ohguro H, Yokoi Y, Ohguro I et al (2004) Clinical and immunologic aspects of cancer-associated retinopathy. Am J Ophthalmol 137:1117–1119. https://doi.org/10.1016/j.ajo.2004.01.010
11. Finn AP, Thomas AS, Stinnett SS et al (2018) The role of cystoid macular edema as a marker in the progression of non-paraneoplastic autoimmune retinopathy. Graefe's Arch Clin Exp Ophthalmol 256:1867–1873. https://doi.org/10.1007/s00417-018-4084-8
12. Abazari A, Allam SS, Adamus G, Ghazi NG (2012) Optical coherence tomography findings in autoimmune retinopathy. Am J Ophthalmol 153.https://doi.org/10.1016/j.ajo.2011.09.012
13. Pepple KL, Cusick M, Jaffe GJ, Mruthyunjaya P (2013) SD-OCT and autofluorescence characteristics of autoimmune retinopathy. Br J Ophthalmol 97:139–144
14. Tsang SH, Sharma T (2018) Autoimmune retinopathy. Advances in Experimental Medicine and Biology. Springer, New York LLC, pp 223–226
15. Masaoka N, Emoto Y, Sasaoka A et al (1999) Fluorescein angiographic findings in a case of cancer-associated retinopathy. Retina 19:462–464. https://doi.org/10.1097/00006982-199919050-00022
16. Rahimy E, Sarraf D (2013) Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: Evaluation and management. Surv Ophthalmol 58:430–458
17. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF (1976) Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol 81:606–613. https://doi.org/10.1016/0002-9394(76)90125-2
18. Murphy MA, Thirkill CE, Hart WM (1997) Paraneoplastic retinopathy: a novel autoantibody reaction associated with small-cell lung carcinoma. J Neuroophthalmol 17:77–83
19. Guy J, Aptsiauri N (1999) Treatment of paraneoplastic visual loss with intravenous immunoglobulin: Report of 3 cases. Arch Ophthalmol 117:471–477. https://doi.org/10.1001/archopht.117.4.471
20. Maleki A, Lamba N, Ma L et al (2017) Rituximab as a monotherapy or in combination therapy for the treatment of

non-paraneoplastic autoimmune retinopathy. Clin Ophthalmol 11:377–385. https://doi.org/10.2147/OPTH.S120162
21. Shildkrot Y, Sobrin L, Gragoudas ES (2011) Cancer-associated retinopathy: Update on pathogenesis and therapy. Semin Ophthalmol 26:321–328
22. Jabs DA, Nussenblatt RB, Rosenbaum JT et al (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140:509–516
23. McCulloch DL, Marmor MF, Brigell MG et al (2015) ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 130:1–12
24. Igarashi N, Sawamura H, Kaburaki T, Aihara M (2019) Cancer-associated retinopathy developing after 10 years of complete breast cancer remission. Neuro-Ophthalmology 43:36–42. https://doi.org/10.1080/01658107.2018.1460761
25. Makiyama Y, Kikuchi T, Otani A et al (2013) Clinical and immunological characterization of paraneoplastic retinopathy. Investig Ophthalmol Vis Sci 54:5424–5431. https://doi.org/10.1167/iovs.13-11868
26. Adamus G, Aptsiauri N, Guy J et al (1996) The occurrence of serum autoantibodies against enolase in cancer-associated retinopathy. Clin Immunol Immunopathol 78:120–129. https://doi.org/10.1006/clin.1996.0021
27. Gitlits VM, Toh BH, Sentry JW (2001) Disease association, origin, and clinical relevance of autoantibodies to the glycolytic enzyme enolase. J Investig Med 49:138–145
28. Pancholi V (2001) Multifunctional α-enolase: Its role in diseases. Cell Mol Life Sci 58:902–920
29. Adamus G, Karren L (2009) Autoimmunity against carbonic anhydrase II affects retinal cell functions in autoimmune retinopathy. J Autoimmun 32:133–139. https://doi.org/10.1016/j.jaut.2009.02.001
30. Adamus G, Yang S, Weleber RG (2016) Unique epitopes for carbonic anhydrase II autoantibodies related to autoimmune retinopathy and cancer-associated retinopathy. Exp Eye Res 147:161–168. https://doi.org/10.1016/j.exer.2016.05.012
31. Mantel I, Ramchand KV, Holder GE et al (2008) Macular and retinal dysfunction of unknown origin in adults with normal fundi: Evidence for an autoimmune pathophysiology. Exp Mol Pathol 84:90–101. https://doi.org/10.1016/j.yexmp.2007.10.006