



Paraneoplastic syndromes and the retina

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Purpose of review

Paraneoplastic diseases of the retina are rare. Diagnosis can be challenging, and studies on management strategies are limited. The purpose of this review is to summarize our current understanding of the presentation, diagnosis, and management for cancer associated retinopathy, melanoma associated retinopathy, paraneoplastic vitelliform maculopathy, and bilateral diffuse uveal melanocytic proliferation.

Recent findings

Multimodal imaging can aid in the diagnosis of paraneoplastic retinopathies since early fundus findings and symptoms can be nonspecific. No standardized treatment protocol exists with therapies having variable efficacy. Generally, systemic immunosuppression is used with possible concomitant local steroid treatment with improved visual outcomes in some cases.

Summary

Paraneoplastic syndromes affect the retina as an autoimmune response to tumor antigens or to circulating tumor-derived factors. Diagnosis hinges on maintaining high degree of clinical suspicion, and multimodal imaging can also be helpful. Once diagnosis is made, prompt systemic work-up for malignancy is necessary. Limited literature exists to suggest superiority of a single treatment, but management involves treatment of the underlying malignancy and local or systemic immunosuppression and/or antibody removal.

Keywords

and bilateral diffuse uveal melanocytic proliferation, cancer-associated retinopathy, melanoma-associated retinopathy, paraneoplastic syndromes, paraneoplastic vitelliform maculopathy

INTRODUCTION

Paraneoplastic syndromes occur in the setting of systemic malignancy as an autoimmune response to tumor antigens or to circulating tumor-derived factors [1,2]. Paraneoplastic syndromes of the retina include cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic vitelliform maculopathy (PVM), and bilateral diffuse uveal melanocytic proliferation (BDUMP) [1–5].

CAR and MAR are two of the three conditions comprising autoimmune retinopathy (AIR), the other being nonparaneoplastic AIR when systemic malignancy is absent. CAR and MAR, forms of paraneoplastic AIR, are thought to occur when tumor antigens trigger an autoimmune response to retinal proteins via molecular mimicry [3,6,7]. CAR may be more common than MAR, but both are rare [8]. Multimodal imaging, electrophysiologic testing, and serologic antibody testing aids in diagnosis as clinical examination is often unremarkable [9].

PVM and BDUMP have more distinctive clinical findings with serous retinal detachments in both and multifocal, vitelliform lesions in the posterior pole in PVM and multiple pigmented or amelanotic uveal lesions in BDUMP [4,10]. PVM is thought to occur as an autoimmune response to neoplasm when immune cells cross-react with the retinal pigment

epithelium (RPE) [11–13]. BDUMP is believed to occur when circulating tumor-derived factors stimulate melanocytic proliferation [10].

Diagnosis of paraneoplastic retinopathies is challenging. Prompt recognition and referral for workup and management is prudent given the systemic implications.

CANCER-ASSOCIATED RETINOPATHY

First described in 1967 [14], CAR arises when anti-retinal antibodies (ARAs), most often antirecoverin (calcium-binding protein in photoreceptors) [15,16],

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KEY POINTS

- Multimodal imaging can aid in diagnosis of paraneoplastic disorders of the retina, and when suspicion is high, prompt referral for systemic work up for malignancy is important.
- Cancer-associated retinopathy and melanoma-associated retinopathy can present with progressive vision loss out of proportion to exam findings so imaging, particularly electroretinogram, fundus autofluorescence, and visual field, and serum testing for ARAs can help make the diagnosis.
- Paraneoplastic vitelliform maculopathy presents with serous retinal detachments and multiple yellow-white subretinal lesions and has an overall good visual prognosis as the condition typically spontaneously resolves.
- Bilateral diffuse uveal melanocytic proliferation presents with serous retinal detachments, uveal thickening on B scan ultrasonography, and patchy “giraffe-like” pattern of hypo- and hyper-autofluorescence on fundus autofluorescence as well as cataracts, anterior rotation of the ciliary body, iridociliary cysts, and glaucoma.
- No treatment modality is universally agreed upon for paraneoplastic retinopathies, but generally, systemic immunosuppression with steroids, intravenous immunoglobulins, and plasmapheresis or plasma exchange therapy is used with possible concomitant local treatment with variable efficacy.

damage the retina via direct cytotoxicity to photoreceptors segments and direct apoptosis of retinal cells [15,16]. Other retinal proteins targeted by ARAs include alpha-enolase, carbonic anhydrase II, heat shock cognate protein 70 (HSC70), and transducin [17–19].

CAR presents with progressive, subacute vision loss, scotomas, photopsias, and/or nyctalopia. Rods and cones are affected to differing degrees [20]. Early on, visual acuity is preserved relative to peripheral visual field restriction, and fundus appears normal. More advanced disease shows retinal vascular attenuation, diffuse retinal atrophy, RPE changes, and waxy disc pallor with intraocular inflammation less commonly present (Fig. 1a,b) [18]. Notably, the clinical presentation of late-stage CAR is similar to retinitis pigmentosa. The differential diagnosis includes inherited retinal dystrophies, vitamin A deficiency, drug toxicities, and inflammatory conditions. Hence, discussion of review of symptoms, family history, malignancy risk factors, and medication use should be done [3,8]. Small cell lung cancer is most common but other malignancies are breast, uterine, prostate, gastrointestinal, liver, and kidney cancer [8,21*,22,23].

Diagnosing CAR is challenging since half of patients experience visual symptoms before the diagnosis of malignancy [24]. In a patient with unremarkable fundus examination but progressive vision loss, CAR should be considered. Multimodal imaging with visual field testing and electroretinogram (ERG) is helpful in diagnosis [9]. Fundus autofluorescence (FAF) often shows a hyperautofluorescent ring in the macula and less commonly shows a peripapillary hyperautofluorescent ring, speckled foveal hyperautofluorescence, patchy peripheral hyperautofluorescence, and hypo and hyper-autofluorescent perivascular lesions (Fig. 1c,d) [25,26]. Optical coherence tomography (OCT) may show macular edema, outer retinal atrophy, and ellipsoid zone loss (Fig. 1e,f); earlier on, outer nuclear layer thinning may occur in a parafoveal distribution with subfoveal preservation [8,27]. Full-field ERG is very sensitive at detecting CAR and shows rod and cone dysfunction (Fig. 2a) [3,6,8,24]. Visual fields are constricted with central or paracentral scotomas [3] (Fig. 2b,c). Fluorescein angiogram is not helpful in diagnosing CAR but is useful for ruling out other causes [24].

Once there is a high index of suspicion, a CAR antibody panel should be ordered [24]. Testing protocols for ARAs lack standardization as different testing methods exist, and laboratories must select the antibodies of interest [20]. Sensitivity can be increased by combining the Western blot analysis with confirmatory immunohistochemical testing on human retinal flatmounts to confirm localization to retinal structures [8,28]. When identified, ARAs increases suspicion for CAR, but ARAs are nonspecific, existing in normal controls and inflammatory diseases [8,29–31]. Amongst ARAs, antirecoverin antibodies have the highest specificity for CAR [3]. However, the presence of antirecoverin antibodies does not confirm the diagnosis either as these can be found in normal patients and in other ocular diseases [8,29–31].

Patients with clinical, imaging, and serologic confirmation of AIR but no known history of cancer should undergo systemic investigation for malignancy in collaboration with a primary care physician or oncologist with completion of age and sex-appropriate testing (e.g. colonoscopy, mammogram), systemic visceral organ imaging by computed tomography or magnetic resonance imaging scans, and laboratory investigations targeted at the patient's risk factors.

The underlying malignancy should be treated. However, despite treatment and even during cancer remission, CAR can still occur because the blood circulation already has the ARAs [19,24,32*]. Given the rarity of this condition, no standardized treatment protocol exists [24]. Typically, systemic corticosteroids, oral or intravenous (i.v.), are initially used

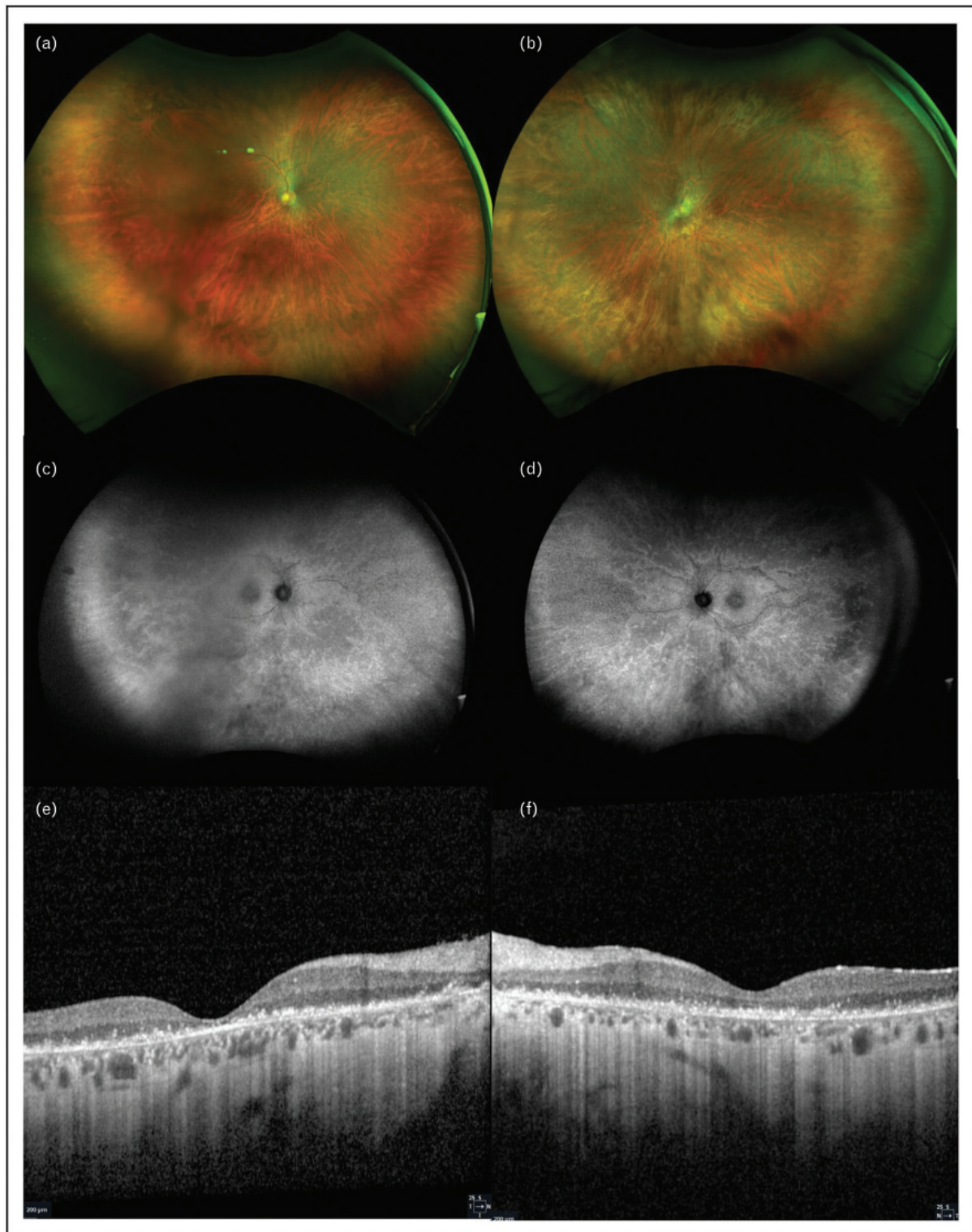


FIGURE 1. A 64-year-old woman presented with bilateral blurry vision for 2 months and was diagnosed with cancer associated retinopathy. Systemic work-up revealed metastatic endometrial carcinoma. Fundus examination of the right (a) and left (b) eye showed optic disc pallor, blunted foveal light reflex, arteriolar attenuation, and retinal pigment epithelium mottling in the periphery. Fundus autofluorescence of the right (c) and left (d) eye showed perivascular hypo-autofluorescence. OCT of the right (e) and left (f) eye showed diffuse outer retinal atrophy.

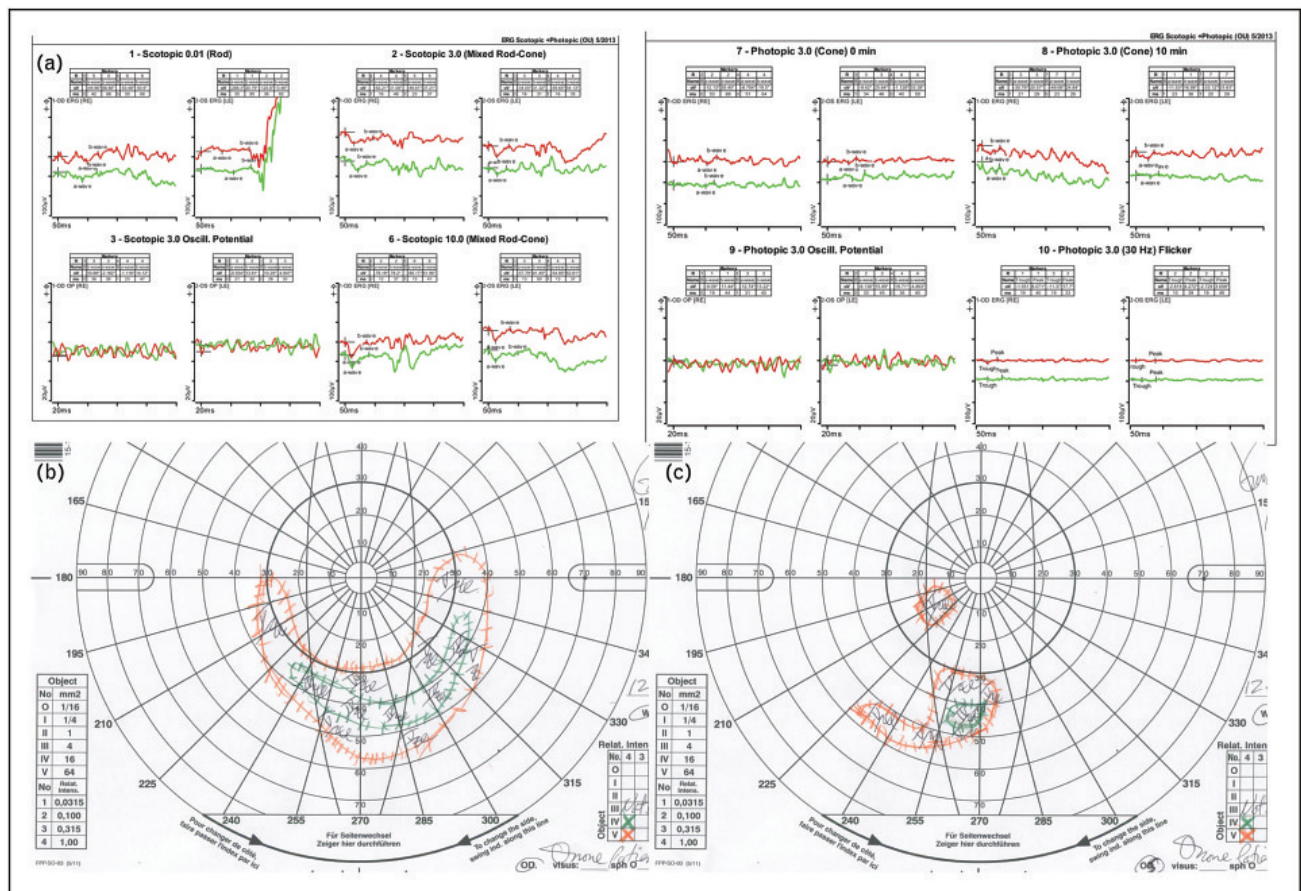


FIGURE 2. The same patient from Fig. 1 with cancer associated retinopathy had full-field electroretinogram (a) done which showed diffuse rod and cone dysfunction. Goldmann visual field for the left (b) and right (c) eye had severely restricted visual fields with a small island of inferior visual field remaining. Serum testing showed positive antirecoverin antibodies. She was treated with a high-dose oral steroid taper, intravenous immunoglobulin, and rituximab. Other treatment options that were discussed with her included dexamethasone injection and plasmapheresis. However, despite treatment, visual acuity remained counting fingers in both eyes.

and can stabilize visual acuity and visual field loss [32[■]]. Steroid sparing agents such as mycophenolate, azathioprine, and methotrexate have stabilized ERG abnormalities in some cases [3,32[■]]. In a meta-analysis of AIR, rituximab, an anti-CD20 monoclonal antibody, was found to stabilize visual acuity and ERG abnormalities [32[■],33], and reports of concurrent rituximab and cyclophosphamide have shown promise [7,34]. A systematic review found that after systemic steroids, intravenous immunoglobulins (IVIg) and plasmapheresis or plasma exchange (PLEX) therapy are the most common therapies used [35,36]. IVIg is more likely to maintain or improve visual acuity relative to untreated patients [35]. In refractory cases, plasmapheresis or plasma exchange (PLEX) therapy, which removes circulating ARAs, has been used [3,7,8,21[■]] but visual improvement may be transient [3]. In one case of early initiation of PLEX therapy 3 weeks following onset of visual symptoms, the patient

had good visual recovery [29]. Combination of these therapies can be effective with one case reporting improved visual acuity and retinal function on ERG after combining i.v. steroids, IVIg, and rituximab [19]. In a meta-analysis by Kapoor *et al.* [32[■]], most patients were treated with systemic therapy; however, local treatment was done if patients could not tolerate systemic therapy. Local corticosteroid treatment can be a good option in patients who are ill, elderly, or with systemic contraindications and has been shown to improve visual acuity [24,37,38]. Huang *et al.* [24] reported improved visual acuity, rod function on ERG, and ellipsoid zone loss on OCT with local treatment only with intravitreal dexamethasone implant followed by 0.18-mg fluocinolone acetonide implant.

The prognosis for CAR depends on tumor origin, disease severity at presentation, timing of treatment initiation, and quantity of circulating ARA titers [21[■]]. OCT and FAF can assess the extent of retinal

atrophy, monitor disease, and predict long-term visual prognosis [9]. Serial ARA testing does not correlate with disease progression or treatment response [8,39]. CAR is often discovered when disease is advanced with significant photoreceptor loss so visual prognosis is often poor with high mortality rate [6]. In a natural history study of untreated patients with AIR, two-thirds experienced progressively worsened vision [35], with worse prognosis for those with antirecoverin antibodies including potentially progressing to no light perception [6].

MELANOMA-ASSOCIATED RETINOPATHY

MAR shares similarities with CAR but occurs in the setting of cutaneous melanoma. In MAR, autoantibodies to a melanoma antigen are thought to cross-react with bipolar cells in the retina. ARAs in MAR include TRPM1, S-arrestin, recoverin, enolase, aldolase A, aldolase C, HSP60, and carbonic anhydrase II with many of these also described in CAR and non-paraneoplastic AIR [40–43].

More common in men with a mean age of 60 (range 30–78) years, MAR presents on average 3.6 years after the diagnosis of cutaneous melanoma, with shorter latency periods in patients with metastatic disease. Rarely, MAR is discovered prior to diagnosis of cutaneous melanoma [40,44]. Patients present with night blindness, shimmering photopias, and visual field constriction with relatively preserved visual acuity and color vision [45,46]. Fundus examination is usually unremarkable early on (Fig. 3). MAR can present with mild vitreous inflammation and in more advanced cases, optic disc pallor, vascular attenuation, and RPE mottling [43,46,47].

The characteristic ERG abnormality is a negative ERG, comprising a preserved A-wave and reduced B-wave with normal photopic but reduced scotopic function [40] (Fig. 4a). Limited conditions cause negative ERG including congenital stationary night blindness, juvenile X-linked retinoschisis, Goldmann-Favre, and Duchenne Muscular Dystrophy. Patients have constriction and central and paracentral scotomas on visual field testing (Fig. 4b,c) [47]. Serum testing for ARAs should be pursued to assist in diagnosis but no ARA specific to MAR has yet been identified [12].

As mentioned, most cases have a known diagnosis of cutaneous melanoma. If the primary cutaneous melanoma is not metastatic, imaging should be done to investigate for metastases [44]. If there is no cancer diagnosis, presence of cutaneous melanoma, uveal melanoma, and mucosal melanoma should be investigated [1,43,45].

Like CAR, management is a joint pursuit of tumor burden reduction, antibody elimination,

and immunosuppressive therapy [45]. Evidence on treatment efficacy is limited, but therapeutic options include systemic corticosteroids, IVIG, and PLEX [45]. Subhadra *et al.* [48] found that IVIG improved visual fields. Systemic immunomodulator therapy can be used but efficacy is unclear as immune checkpoint inhibitors commonly used to treat metastatic cutaneous melanoma can also cause autoimmune eye disease and worsen retinopathy [49,50]. Local treatment may also be considered, as intravitreal steroid injections have improved visual symptoms, visual field, and ERG parameters [49,51] while simultaneously reducing the intraocular inflammatory effects of immune checkpoint inhibitors [52]. Hamdan *et al.* [53] described a case of full recovery of visual acuity and ERG following combination of rituximab, IVIG, and intravitreal corticosteroids. The prognosis of MAR depends upon early diagnosis and treatment initiation to limit irreversible damage to retinal bipolar cells [45].

PARANEOPLASTIC VITELLIFORM MACULOPATHY

PVM, occurring in the context of malignancy, is a form of acute exudative polymorphous vitelliform maculopathy (AEPVM) which can also be secondary to other causes [54]. PVM is hypothesized to occur when immune cells triggered by malignancy cross-react with the RPE, impairing RPE phagocytosis, resulting in lipofuscin accumulation, photoreceptor outer segment shedding, and serous retinal detachments [54,55]. Auto-antibodies have been identified against peroxiredoxin 3 (PRDX3), bestrophin 1, and other RPE components [11,12,56]. PVM is usually associated with cutaneous melanoma and secondarily choroidal melanoma but other malignancies like breast carcinoma, lung adenocarcinoma, and clear cell sarcoma have been reported [54,57]. Typically occurring after cancer diagnosis, one review described PVM developing 2–23 years following enucleation for choroidal melanoma [57]. In many cases, PVM indicates metastatic disease [58,59].

Patients often experience acute bilateral blurry vision and headaches [55,60]. Classically, examination shows serous retinal detachments and multiple yellow-white subretinal lesions of variable morphology in the posterior pole. However, if caught early, only serous retinal detachments may be present as subretinal lesions may require at least 1 month of follow-up before being observable [61]. As subretinal fluid (SRF) resorbs, polymorphous yellow vitelliform deposits accumulate and start in a honeycomb pattern along the arcades before coalescing and forming a larger, curvilinear pseudo-hypopyon which are hyperautofluorescent on FAF [13,56,60,62]. OCT demonstrates serous retinal

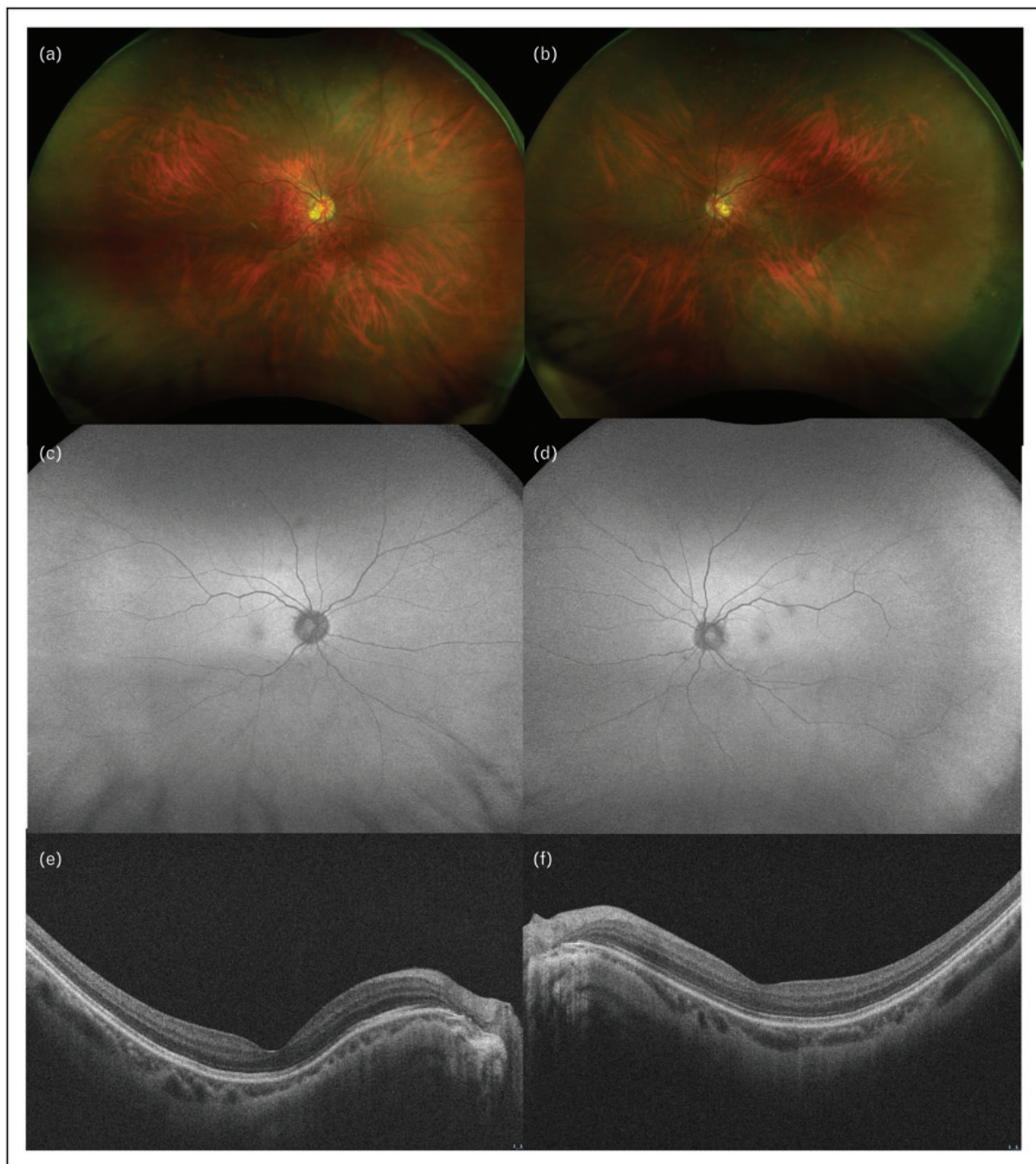


FIGURE 3. A 58-year-old man with metastatic cutaneous melanoma treated with immune checkpoint inhibitors diagnosed with melanoma-associated retinopathy after presenting with subacute vision loss of the right eye. Fundus photography of the right (a) and left (b) eye showed myopic peripapillary atrophy and fundus autofluorescence of the right (c) and left (d) eye was unremarkable. Optical coherence tomography of the right (e) and left (f) eye showed myopic contour but no outer retinal loss or cystoid macular edema.

detachments and may show intraretinal cysts in the inner and outer nuclear layers or intraretinal hyper-reflective deposits [56,60]. Fluorescein angiogram may show mildly hyperfluorescent areas corresponding to the vitelliform lesions and serous retinal detachments or blocked fluorescence from large accumulations of

subretinal material [13,60]. EOG is abnormal [11,62]. ERG may be normal or show rod or cone dysfunction [29,54,61,63].

In a patient with AEPVM, a comprehensive work-up is usually performed to rule out other infectious and autoimmune causes. Assuming work up is negative,

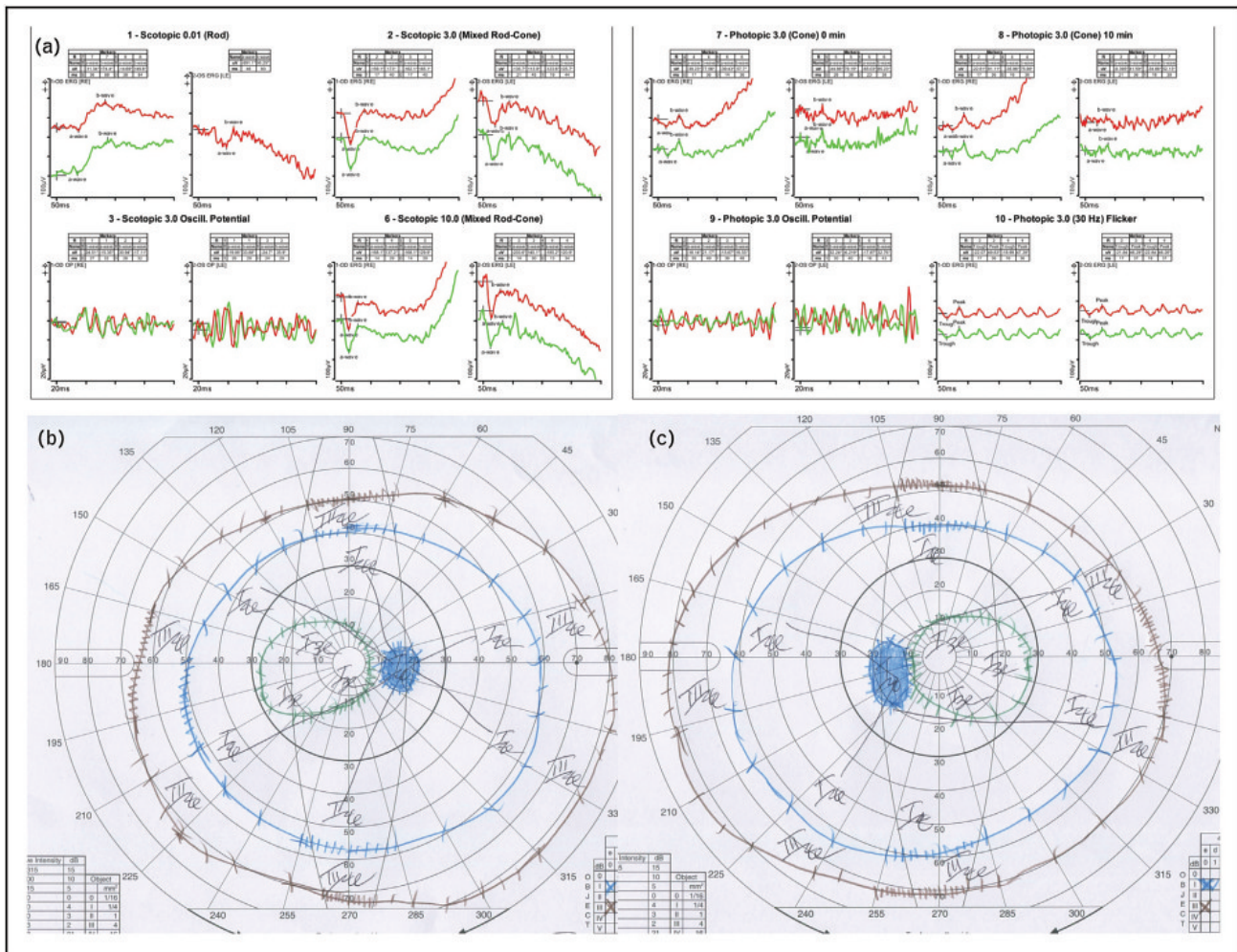


FIGURE 4. The same patient from Fig. 3 with melanoma associated retinopathy had full-field electroretinogram (a) which showed rod and cone dysfunction, with clear electronegative configuration in the left eye and relative electronegative configuration in the right eye. Goldmann visual field of the right (b) and left (c) eye showed loss of central isopter sensitivity but relatively full peripheral visual fields. Serum testing found antibodies to aldolase, enolase, arrestin, and PKM2. The patient was treated with sub-tenon triamcinolone injection in both eyes. Most recent visual acuity was 20/50 and 20/150 in the right and left eye, respectively.

age- and gender-appropriate screening for malignancy should be considered, including thoracoabdominal imaging and dermatologic screening [29].

Visual prognosis is favorable as ocular disease often improves spontaneously [63]. Even if ERG still shows persistent abnormalities, visual acuity usually improves as SRF resolves [64]. Evidence is insufficient to identify the efficacy of early systemic or intraocular immunosuppression [62,65–67]. Recovery does not seem to be significantly impacted by intravitreal corticosteroids tried for intraretinal edema [65]. With secondary choroidal neovascularization, antivascular endothelial growth factor (anti-VEGF) is used to decrease vascular leakage and control disease progression [62,68]. Gao *et al.* [66] reported a case of visual acuity improvement and resolution of SRF

following adjuvant intravitreal methotrexate along with systemic treatment of the underlying malignancy; the eye treated with intravitreal methotrexate showed greater improvement in visual acuity and edema on OCT compared to the untreated eye [66].

BILATERAL DIFFUSE UVEAL MELANOCYTIC PROLIFERATION

First reported by Machemer in 1966 [61], BDUMP is currently hypothesized to occur via cultured melanocyte elongation and proliferation (CMEP), a tumor-secreted factor which stimulates diffuse melanocytic proliferation within the choroid, ciliary body, and iris causing damage to the RPE and outer retina [69,70[¶]].

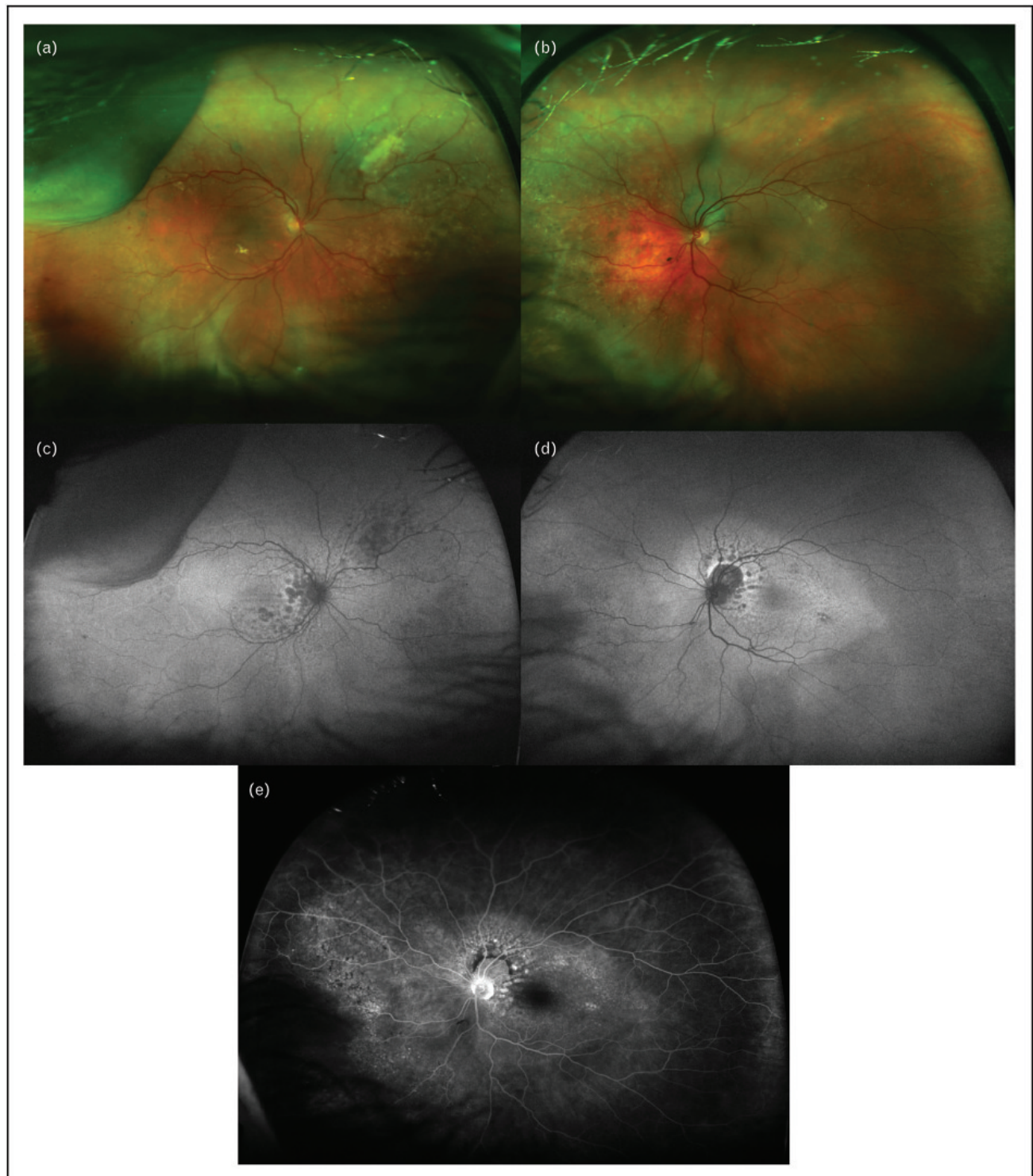


FIGURE 5. An 80-year-old woman without known malignancy was referred for vision loss and bilateral cataracts and diagnosed with bilateral diffuse uveal melanocytic proliferation. Wide-field fundus photography of the right (a) and left (b) eye showed a superotemporal exudative retinal detachment in the right eye, prominent serous choroidal detachments in both eyes, and melanocytic choroidal lesions in both eyes, including a larger peripapillary choroidal lesion in the left eye. Fundus autofluorescence of the right and left eye showed alternating patchy hypo- and hyper-autofluorescence in both eyes (c,d). Fluorescein angiography (e) of the left eye showed an inverse pattern of this classic “giraffe-like” pattern on fundus autofluorescence.

Patients present with progressive bilateral blurry vision. Historically, the five cardinal signs of BDUMP were multifocal, round/oval, red-orange, subretinal patches, corresponding to hyperfluorescent pattern on FA, multiple, elevated uveal melanocytic tumors and diffuse thickening of the uveal tract (Fig. 5 a,b), exudative retinal detachment, and rapid cataract progression [71]. Other findings include shallow anterior chamber, glaucoma from anterior rotation of the ciliary body, dilated episcleral vessels, iridocyclitis, iris and ciliary body cysts, and iridodonesis [72,73].

More recently, Sarigul Sezenoz *et al.* [74^{***}] described novel multimodal imaging findings in

BDUMP. Ultra-wide fundus photography showed diffuse reticular orange pigment patches and speckled pigmentary changes in the posterior pole with pigmentary changes progressing to the mid-periphery and periphery later in the disease. Vessel attenuation was also seen late in disease [74^{***}]. The most prominent finding on fluorescein angiogram and FAF is the classic “giraffe-like” pattern with patchy alternating hypo and hyper-fluorescence and autofluorescence, respectively (Fig. 5c–e) [70^{*},75]. OCT most commonly shows SRF and subretinal hyperreflective material (Fig. 6a–c); other findings include elongated photoreceptor outer segments, ellipsoid zone and RPE loss with adjacent



FIGURE 6. Optical coherence tomography (OCT) of the right (a) and left (b) eye showed macular subretinal fluid in both eyes with subretinal hyperreflective material. (c) Enhanced depth imaging-OCT of the left eye showed presence of a choroidal lesion and choroidal thickening from infiltration .

thickened zones, and diffuse intraretinal hyperreflective foci in all inner and outer retinal layers [74[■],75,76]. B scan ultrasonography shows low reflective choroidal thickening and multifocal, exudative retinal detachments (Fig. 7a,b) [74[■]]. Ultrasound biomicroscopy is also required as may demonstrate ciliary body thickening or detachments, iridociliary cysts, and angle closure (Fig. 7c–f) [74[■]].

Urgent oncology referral for malignancy work-up is warranted, as half of patients with BDUMP present prior to diagnosis of systemic malignancy

[76]. The most common cancers are ovarian and uterine in women and lung in men [77]. Again, treatment of the malignancy is required but no standardized treatment for ocular disease exists. Some case reports describe PLEX as having the greatest efficacy in preventing disease progression by removing serum immunoglobulin G which stimulates melanocytes, although vision improvement may be temporary [70[■],76]. One case of high-dose IVIG did restore vision and maintained sustained improvement [78]. Most case reports of BDUMP still have poor visual prognosis, though IVIG and PLEX is

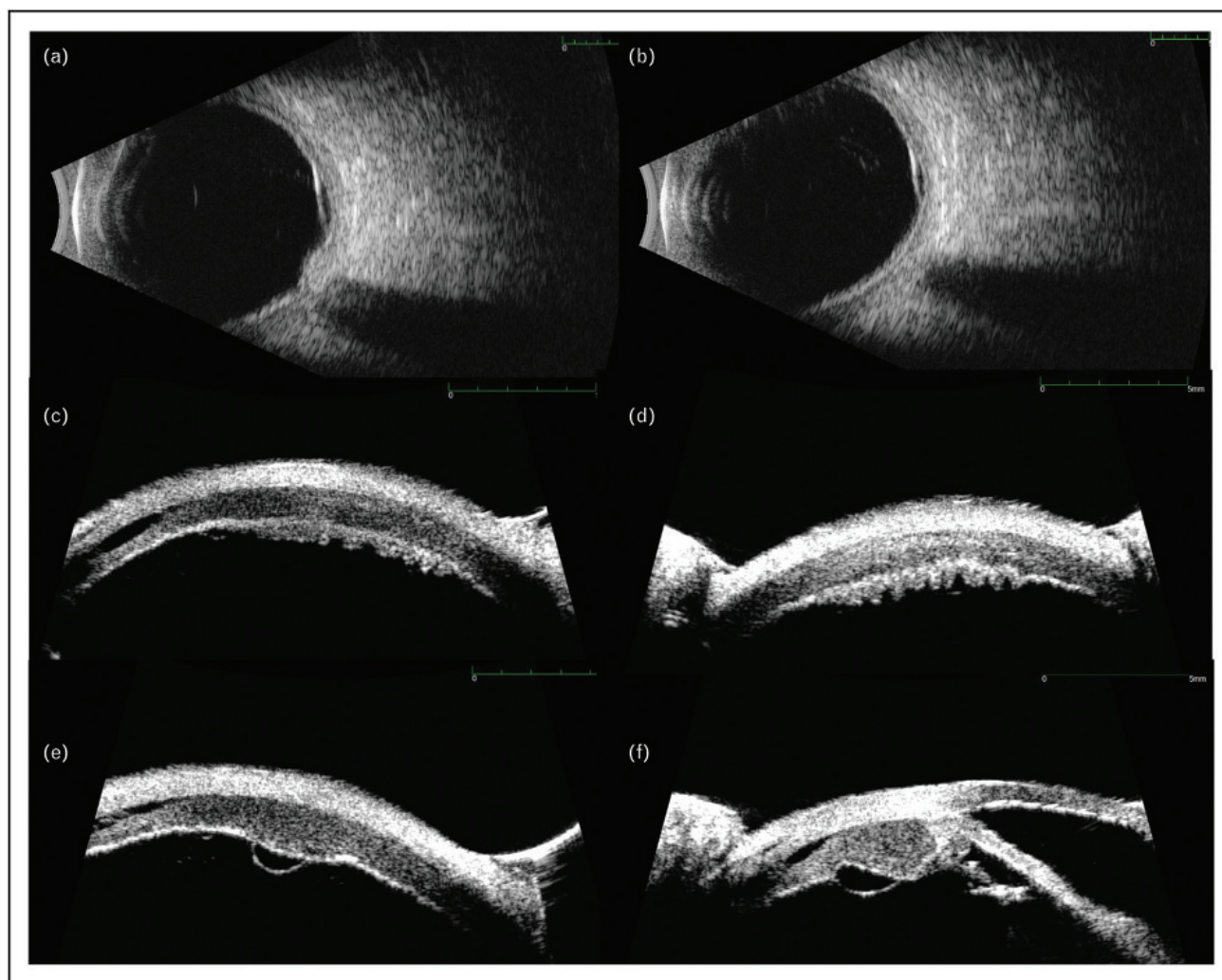


FIGURE 7. A different case of bilateral diffuse uveal melanocytic proliferation in a 71-year-old man, subsequently diagnosed with lung adenocarcinoma. B-scan ultrasonography of the right (a) and left (b) eye demonstrated low reflective choroidal thickening and multifocal, serous retinal detachments. Ultrasound biomicroscopy of the right (c) and left (d) eye revealed ciliary body thickening and ciliary cysts associated with anterior thickening of the ciliary body in the right (e) and left (f) eye. The patient was treated with nine cycles of chemotherapy for his lung adenocarcinoma and plasmapheresis for his ocular disease. His final visual acuity was 20/25 and 20/30 in the right and left eye, respectively, with resolution of the subretinal fluid one year after initial presentation.

thought to stabilize disease [73]. Other treatments have been done to treat SRF, including intravitreal anti-VEGF, local and systemic steroids, intravitreal methotrexate, oral acetazolamide, and orbital radiotherapy [79–81]. Cataract surgery can be considered, although peri-operative systemic, intravitreal, and topical steroids should be considered to mitigate a significant fibrin reaction postoperatively [73]. Despite treatment of the malignancy, overall prognosis is poor with mean survival rate of 12–15.7 months after presentation [76].

CONCLUSION

Early recognition of paraneoplastic retinopathies allows prompt management of systemic malignancy and ocular disease. High degree of clinical suspicion should be maintained in the cancer patient with unexplained vision loss or degree of vision loss that does not align with overall clinical findings. Multimodal imaging is helpful in diagnosis. CAR and MAR present with progressive visual symptoms that may be out of proportion to fundus findings. OCT, visual field, ERG, and serum ARA testing are useful in diagnosing CAR and MAR. PVM presents with vitelliform lesions and serous retinal detachments with relatively good visual prognosis. BDUMP typically presents with serous retinal detachments, rapidly progressive cataracts, diffuse uveal thickening, and a distinctive patchy giraffe pattern of hyper and hypo-autofluorescence on FAF. Overall, evidence on treatment efficacy is limited by the rarity of these conditions, but generally, in addition to treatment of the malignancy, systemic immunosuppression with adjuvant local ocular therapy is used. Further studies are needed to develop a standardized treatment protocol for paraneoplastic disorders of the retina.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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