Review Article

Paraneoplastic retinopathies: an update on pathogenesis, diagnosis and management

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Abstract: The paraneoplastic retinopathies are a heterogeneous group of disorders with significant visual consequences occuring in the setting of a systemic malignancy. These conditions may be characterized by the presence of antiretinal antibodies and may predate or follow the diagnosis of an underlying malignancy. Herein I review the clinical findings, pathophysiology, laboratory testing and management of the paraneoplastic retinopathies: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), bilateral diffuse uveal melanocytic proliferation (BDUMP) and paraneoplastic vitelliform maculopathy (PVM). The pathophysiology of the paraneoplastic retinopathies varies from molecular mimicry resulting in anti-retinal antibody production (CAR, MAR) to relases of soluble factors either by the primary tumor (BDUMP) and/or immune system in response to the primary tumor (PVM) which result in retinal and/or retinal pigment epithelium dysfunction. For each condition, structural and functional multimodal retinal testing can be helpful in establishing the diagnosis. Treatment for the paraneoplastic retinopathies involves a combination of treating the underlying malignancy plus additional local and/or systemic immunosuppressive agents though no systemic therapeutic protocols exist. Despite these interventions, the retinopathy may be progressive or the retinopathy may be a harbinger of poor survival. Nevertheless, prompt diagnosis may help identify an underlying malignancy earlier and may thus improve cancer-related survival.

Keywords: Paraneoplastic; retinopathy; bilateral diffuse uveal melanocytic proliferation (BDUMP); cancer-associated retinopathy (CAR); vitelliform

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Introduction

Paraneoplastic syndromes are rare conditions with a variety of systemic manifestations secondary to an underlying malignancy. Broadly speaking, paraneoplastic syndromes manifest remotely from the site of malignancy and occur secondary to substances produced by cancerous cells—hormones, peptides or cytokines—or immune-mediated molecular mimicry between cancerous antigens and normal tissue (1,2). Paraneoplastic syndromes have been reported in as much as 10% of cancer patients but the prevalence of paraneoplastic syndromes affecting the retina remains unknown (3). The paraneoplastic retinopathies include cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), bilateral diffuse uveal melanocytic proliferation (BDUMP) and paraneoplastic vitelliform maculopathy (PVM). Herein I will review the pathophysiology, clinical findings, multimodal ocular imaging and functional testing, diagnostic testing and treatment paradigm for the various paraneoplastic retinopathies.

CAR

CAR, otherwise known as paraneoplastic autoimmune retinopathy (pAIR) was first described by Sawyer *et al.* in 1976 in a series of 3 patients with lung cancer suffering from concomitant vision loss and retinal degeneration (4). The retinal degeneration seen in CAR is thought to be secondary to circulating auto-antibodies which cross-react with tumor-specific and retina-specific antigens. This pathophysiology

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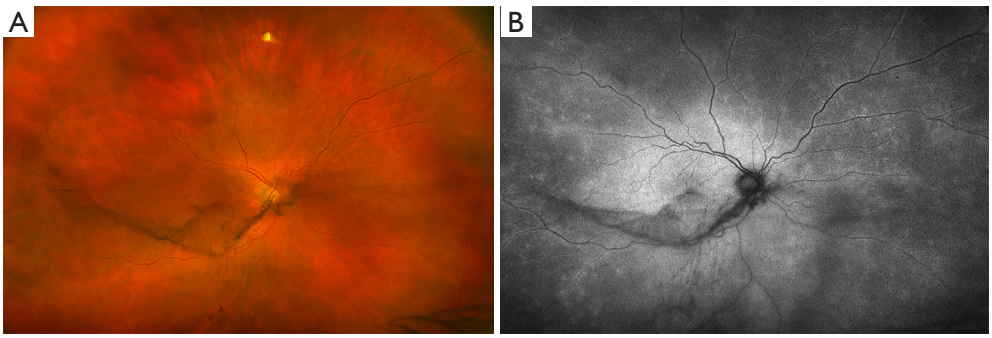

Figure 1 Pseudocolor photo (A) and fundus autofluorescence (B) in a patient with cancer-associated retinopathy. Note the presence of vitreous debris on the pseudocolor photo. Autofluorescence reveals ill-defined hyperautofluorescence in the macula and along the retinal blood vessels.

of CAR was proposed by Keltner *et al.* in 1983 when the group found circulating anti-retinal antibodies in a patient with cervical lymphoma and progressive vision loss (5). The most common primary tumor accounting for the vast majority of cases of CAR is small cell lung cancer, breast cancer or a gynecologic malignancy (6-8). A variety of other solid-tumor associations including non-small cell lung, thyroid, thymus, colon, bladder, pancreatic and hematologic malignancies have also been associated with CAR (6-8). In a series of 209 patients with CAR, Adamus reported an average age of presentation of 65 years with a 2:1 female to male predilection (8). In the same series, the time from cancer diagnosis to onset of CAR varied from weeks to years depending on the type of primary malignancy. That being said, visual symptoms may precede the diagnosis of the underlying malignancy in almost half of patients (6,7).

Vision loss in CAR is typically rapid, painless and may feature light-sensitivity, photopsias, glare, nyctalopia, loss of peripheral and/or central vision, loss of color vision. Visual symptoms in CAR represent widespread dysfunction of both rods and cones though there is a rare variant of CAR which only affects cones (6). Fundus findings in CAR are classically unimpressive relative to the extent of visual symptoms. In more advanced disease there may be retinal vascular attenuation, optic disc pallor and retinal pigment epithelial (RPE) changes. Also variably present are mild vitritis, anterior uveitis, retinal vasculitis and cystoid macular edema (CME) (*Figure 1*).

Structural and functional multimodal retinal testing can be helpful in establishing the diagnosis of CAR. Optic coherence tomography (OCT) often reveals significant macular outer retinal atrophy with loss of the ellipsoid zone and thinning of the outer nuclear layer (*Figure 2*) (9). CME and schisis-like changes may also be variably present. Fluorescein angiography (FA) is usually unremarkable except in cases featuring a mild vasculitis in which perivascular leakage may be evident. Fundus autofluorescence (FAF) can be very useful in following the progression of CAR. FAF typically reveals hyperautofluorescence in the region of outer retinal loss essentially from a window defect revealing retinal pigment epithelium (RPE) fluorophores (*Figure 1*) (10). There may often be a ring of hyperautofluorescence corresponding to the region of outer retinal loss in the macula. With more longstanding diseases, there may also be regions of hypoautofluorescence corresponding to areas of combined outer retinal and RPE death. Visual field abnormalities range from central, cecocentral, paracentral or arcuate defects to ring scotomata or generalized depression (11). Electroretinography (ERG) findings in CAR are representative of global rod and cone dysfunction with attenuated or completely extinguished photopic and scotopic responses (12). ERG may additionally show selective bipolar cell dysfunction in some cases. Despite the array of findings on multimodal retinal diagnostics, there are no specific diagnostic criteria for CAR. The diagnosis thus relies on clinical and ERG findings of retinal degeneration in combination with a diagnosis of a systemic malignancy, circulating anti-retinal antibodies and no alternate etiologies to explain global retinal dysfunction such as a hereditary retinal degeneration.

Laboratory testing in cases of suspected CAR should focus on ruling out masquerades such as syphilis and checking for serum anti-retinal antibodies. The first anti-retinal antibody identified in a patient with small cell lung cancer and CAR was against the 23-kDa antigen, recoverin (13). Recoverin, when present, is now known to

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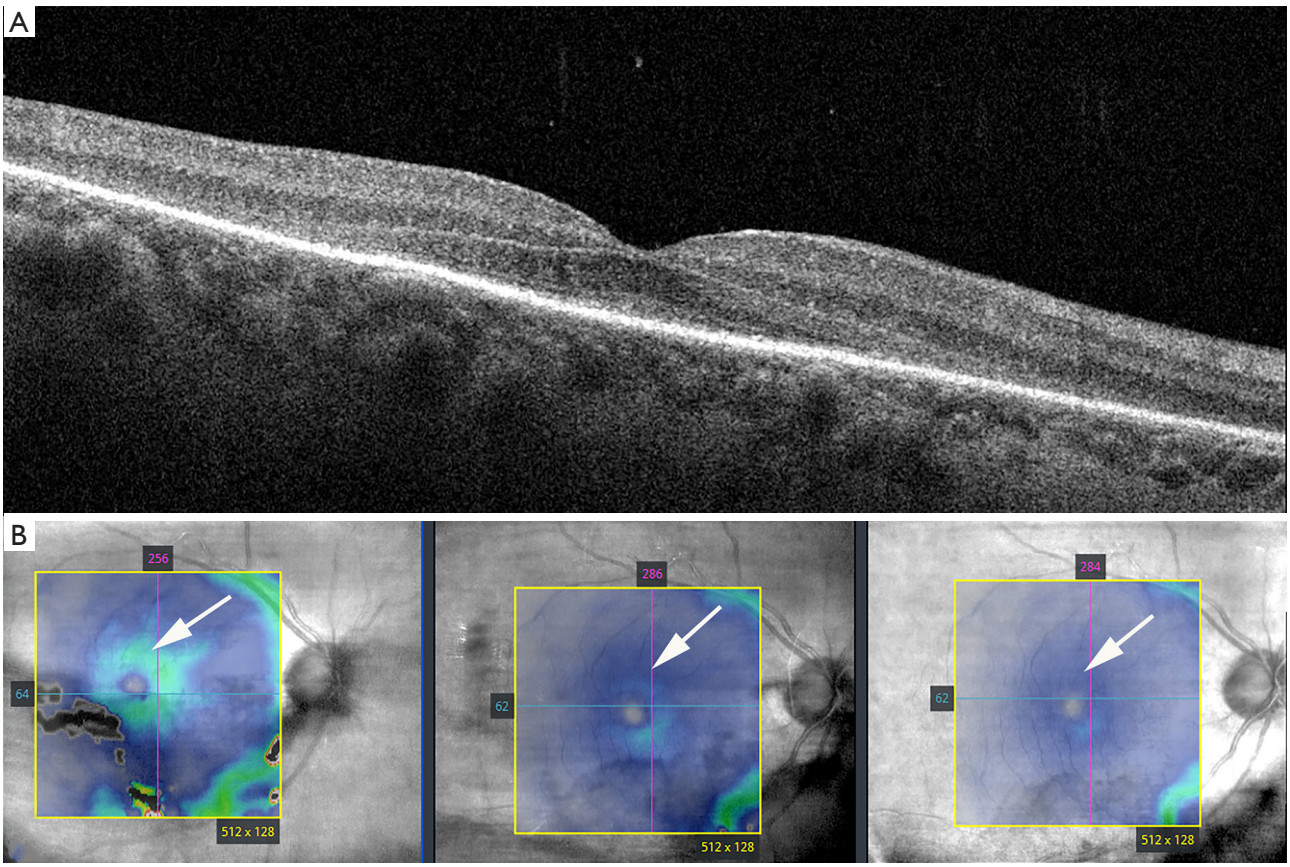

Figure 2 Optical coherence tomography in a patient with cancer-associated retinopathy. The horizontal line scan (A) reveals loss of outer retinal layers with some foveal sparing. The series of retinal thickness maps over a 3-month period (B) showing progressive retinal thinning as evidenced by change in color in the perifoveal region from green to blue (arrows).

be the most sensitive and specific antigen found in CAR. The reported prevalence of anti-recovering antibodies in CAR is 5% (14). Recoverin is a calcium-binding protein found in photoreceptors where it regulates phosphorylation of rhodopsin. Recoverin has been found to be abnormally expressed in tumor cells of patients with CAR. There are numerous other antigens identified in CAR including carbonic anhydrase II (CAII, 30 kDa), transducin- α (40 kDa), α-enolase (46 kDa), arrestin (48 kDa), tubby-like protein 1 (TULP1, 78 kDa) amongst others (14). Adamus and colleagues have proposed that anti-retinal bodies against each of these specific antigens accounts for the phenotypic heterogeneity seen in CAR (8). For example, antibodies against α-enolase target ganglion cells and inner retinal layers and cones while antibodies against transducin- α target rods and ganglion cells which explains the phenotypic variation in an anti- transducin-α retinopathy (loss of night vision, peripheral vision) compared to an anti-α-enolase retinopathy (loss of central and color vision). Both anti-transducin-α retinopathy and anti-α-enolase retinopathy can result in secondary optic nerve atrophy secondary to ganglion cell dysfunction (8).

Presence of anti-retinal antibodies alone is insufficient to diagnose CAR. Anti-retinal antibodies have been detected in normal controls as well as in patients with other ocular diseases (14-16). Additionally, the concordance rate between laboratories checking for anti-retinal antibodies has been shown to be as low as 36% which has been attributed to non-standardized laboratory practices (17,18). There is currently only one Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory in the United States for anti-retinal antibody testing. Recently, Chen and colleagues reported on a series of 14 patients without autoimmune retinopathy whose sera was evaluated for anti-retinal antibodies at this CLIA-certified lab (19). Despite standardized testing protocols, 13/14 patients (93%) tested

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positive for a median of 5 anti-retinal antibodies. The authors attempted to replicate the results at the Mayo Clinic Neuroimmunology Research Laboratory using similar methodology and found that all 14 patients tested positive for a median of 7 anti-retinal antibodies with a concordance rate of 57%. None of the patients in this study tested positive for recoverin. Given these data, I only test for retinal antibodies in patients with a high suspicion for CAR and other than the presence of antibodies against recoverin, I find positive anti-retinal antibody testing to be of limited clinical utility.

No standardized treatment protocol has been shown to be uniformly effective in cases of CAR. Importantly, treatment of the underlying cancer alone does not prevent visual decline. The basis for the treatment of CAR is long-term immunosuppression with or without adjunctive local steroids (20). In a series of 33 patients with CAR, oral and IV corticosteroids were shown to result in improvement in visual function in 62% of patients (20). In addition to systemic steroids (21), intravenous immunoglobulin (IVIg) (22). and steroid-sparing immunosuppressive agents such as mycophenolate mofetil, azathioprine, cyclosporine, rituximab (anti-CD20 antibody) and alemtuzumab (anti-CD52 antibody) have been reported to be used in cases of CAR with some success (9,23,24).

Ferreyra *et al.* (15) and Huynh *et al.* (25) have reported on improvement in visual function in patients with CAR using repeated local corticosteroid injections alone. In both cases systemic immunosuppression was either ineffective or not tolerated. Local steroids thus remain an important adjunct in the management of CAR, especially when CME is present. Despite the use of an aggressive immunosuppressive regimen, vision function in CAR often does not recover and in many cases will continue to decline. Additionally, the impact of a potent immunosuppressive regimen on cancer-related mortality needs to be considered.

MAR

MAR, a subtype of CAR, was first reported in a case report from 1988 wherein a 69-year-old patient developed sudden onset nyctalopia and photopsias 3 years following resection of a cutaneous malignant melanoma (26). Unlike CAR, most cases of MAR have a known history of malignant melanoma and in some cases herald metastatic disease. Most of the initial cases of MAR were found in association with cutaneous melanoma but it has since been described in ciliochoroidal melanoma and mucosal melanoma. In a series of 62 patients with MAR, Keltner *et al.* found an average latency period of 3.6 years (range, 2 months to 19 years) from the diagnosis of melanoma to onset of MAR (27). The same series found a male preponderance to the development of MAR with the male to female ratio being 4.7:1 despite no such disproportionate predilection of males to cutaneous melanoma.

Typical symptoms of sudden-onset nyctalopia and bilateral photopsias reflect rod dysfunction. Clinical findings and multimodal retinal structural and functional testing are similar to CAR with a few notable exceptions:

(I) Presenting visual acuity is typically better in MAR than CAR. In the report by Keltner *et al.*, 28/34 patients (82%) had visual acuity of 20/60 or better at presentation (27).

(II) MAR has historically been thought to be secondary to anti-retinal antibodies affecting bipolar cells. Two independent reports analyzing the sera of patients with MAR identified antibodies against the transient receptor potential cation channel, subfamily M, member 1 [TRPM1, also known as melastatin 1 (MLSN1)] (28,29). TRPM1 is the cation channel responsible light response in retinal ON bipolar cells and is specifically expressed in these bipolar cells (28,29). Mutations in TRPM1 are also responsible for some forms of congenital stationary night-blindness (CSNB) (30), which explains the similarity between features of MAR and CSNB. That being said, several other anti-retinal antibodies have been identified in MAR thus leading to the heterogeneity of the disease as seen in CAR.

(III) The ERG in MAR is classically electronegative. This features a normal dark-adapted a-wave followed by a markedly depressed b-wave (6). This indicates normal photoreceptor function but disruption of either bipolar cells or transmission between photoreceptors and bipolar cells.

Data on treatment options in MAR are limited to case reports and case series. While there is no consensus treatment regimen for MAR, the initial steps are cytoreduction of metastatic disease with surgery, chemotherapy, and/or radiation followed by IVIg (27). Despite these interventions, the impact on visual outcomes has been underwhelming. In the series from Keltner *et al.*, only 7/62 patients (11%) experienced some visual improvement after some combination of the above therapies. The role of immunosuppression in MAR is unclear but there is naturally a concern that suppression of the tumor surveillance function of the immune system with known metastatic melanoma could worsen survival.

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Systemic corticosteroids are largely ineffective in MAR though there has been some data to support the use of local steroids especially in cases featuring CME, vitritis or retinal vasculitis. There was recently a case reported by Karatsai *et al.* in which a patient with MAR was treated with bilateral intravitreal fluocinolone acetonide steroid implants (31). Three years post-implantation, the patient's vision remained 20/20 in each eye with part resolution of baseline ERG abnormalities.

BDUMP

The term BDUMP was first coined by Barr *et al.* in 1982 to describe clinical findings in four patients with unusual bilateral proliferation of uveal melanocytes resembling multifocal bilateral uveal melanomas (32). Each case had a concomitant systemic malignancy. The authors noted a case with similar clinical findings reported by Machemer in 1966 (33). BDUMP was further elaborated on by Gass *et al.* to include vision loss accompanied the following cardinal signs (34):

(I) Multiple round or oval subtle red patches at the level of the RPE in the posterior fundus (*Figure 3*).
(II) Striking pattern of multifocal areas of early hyperfluorescence on FA corresponding to these patches (*Figure 3*).
(III) Development of multiple, slightly elevated, pigmented and nonpigmented uveal melanocytic tumors and diffuse thickening of the uveal tract.
(IV) Exudative retinal detachment.
(V) Rapid progression of cataracts.

Gass *et al.* noted that the first two cardinal signs often antedate the following three. Since then, dozens of cases of BDUMP have been reported with most patients being diagnosed in the sixth and seventh decade (34). The majority of associated malignancies in women are urogenital cancers, while in men, lung cancers are most common. The diagnosis of BDUMP often antedates the diagnosis of a systemic malignancy in about half of affected patients with the average survival after the diagnosis of BDUMP being 15 months (35-37).

In addition to the cardinal features described above, eyes with BDUMP have been noted to have a "giraffe pattern" to their fundus reflective of circular or polygonal patches of RPE atrophy with surrounding orange zones of RPE hypertrophy. The patches of RPE atrophy are responsible for the characteristic window defects seen on FA. OCT similarly shows areas of RPE hypertrophy and RPE loss. FAF will typically show hypoautofluorescence in region of RPE atrophy with intervening hyperautofluorescence in region of RPE hypertrophy (*Figure 3*).

While the mechanism is unclear, the primary tumor in BDUMP stimulates proliferation of uveal melanocytes. One hypothesis is that the primary tumor secretes melanocytic growth factors. This is supported by the observation that about 25% of patients with BDUMP develop skin or mucous membrane hyperpigmentation (38). Additionally, one study found that serum and plasma from some patients with BDUMP caused proliferation of cultured human melanocytes (39).

A review of 68 cases of BDUMP from the literature published in 2016 showed modest visual improvement with various therapeutics (40). In 9/68 patients, treatment was directed only at the primary malignancy which resulted in improved visual function in 5/9 patients. Most patients in the series received local or systemic corticosteroids either alone or in combination with other modalities such as anti-vascular endothelial growth factor (anti-VEGF) therapy or radiation. These therapeutic options did not appear to show any benefit. As of 2020 there have been approximately 20 published cases of BDUMP treated with plasmapheresis of which 13 were reported to have some improvement in visual function (35). Given the high rate of mortality in BDUMP, long-term data on the efficacy of any specific treatment modality is lacking.

PVM

PVM has been described under multiple names including paraneoplastic vitelliform retinopathy and acute exudative paraneoplastic polymorphous vitelliform maculopathy (AEPPVM). PVM is a form of vitelliform disease characterized by acute, often bilateral vision loss with associated multifocal vitelliform retinal lesions occurring in the setting of a known malignancy (*Figure 4*). It was initially thought to occur most often in patients with a melanoma, but has also been observed in patients with other malignancies as well (41,42). The diagnosis of PVM may follow the diagnosis of the primary tumor by years. That being said, PVM not only appears to correlate with the presence of metastatic disease but the severity of PVM may correlate with the metastatic disease burden (41-43).

Patients may complain of vision loss, photopsias, metamorphopsia, glare, halos and/or nyctalopia. Funduscopy typically reveals bilateral multifocal yellow-orange vitelliform lesions with associated low serous retinal detachments. OCT reveals an accumulation of

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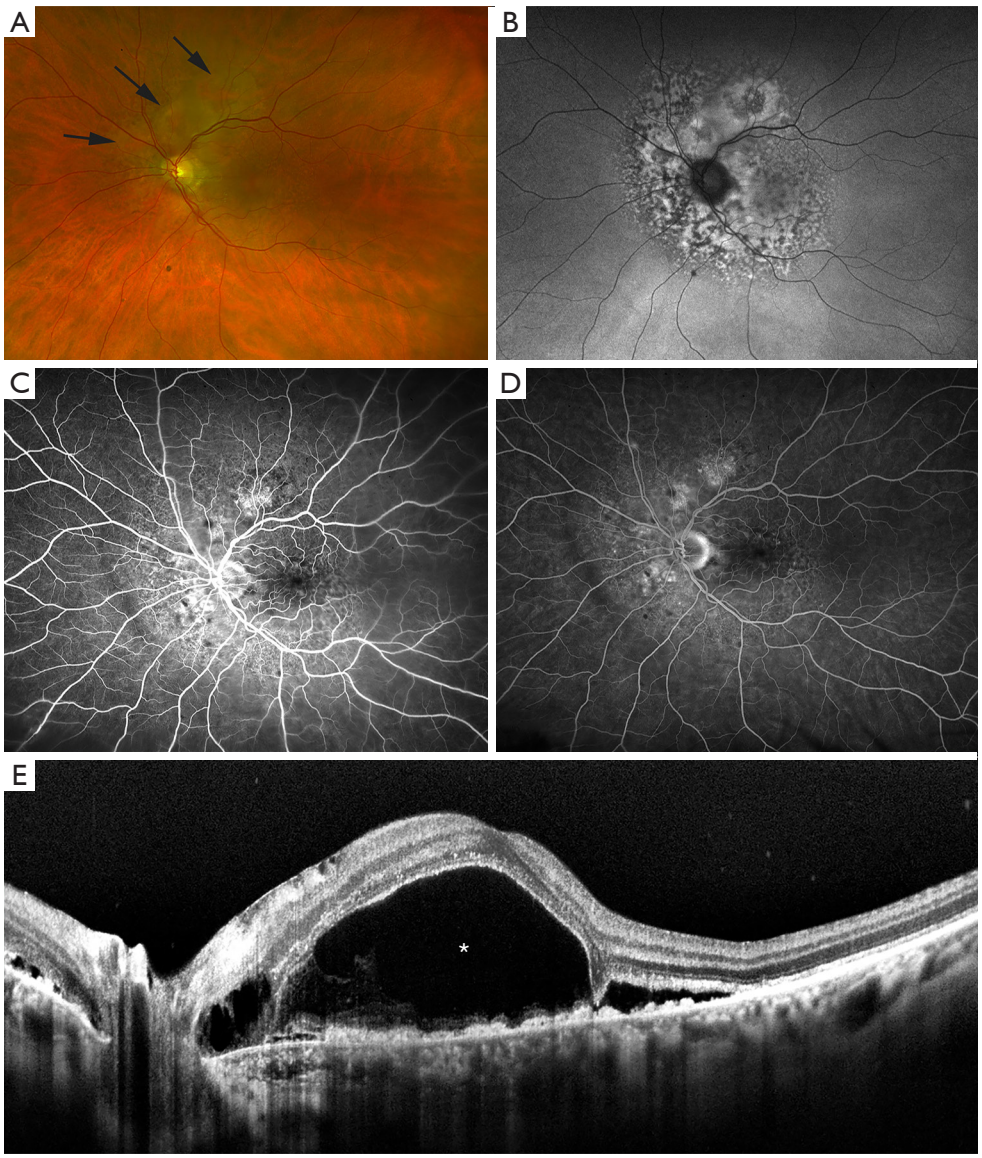

Figure 3 Multimodal imaging in a patient with bilateral diffuse uveal melanocytic proliferation. The pseudocolor photo (A) reveals multiple orangish-red patches in the posterior fundus (arrows). Fundus autofluorescence (B) shows a dramatic pattern of mixed hyperautofluorescence with intervening hypoautofluorescence. Early (C) and late (D) frames of fluorescein angiography reveal few areas of blockage and window defects with subsequent staining. Optical coherence tomography (E) shows thickening of the retinal pigment epithelium with overlying pockets of subretinal fluid (asterisk).

hyperreflective material in the subretinal space as well as hyporeflective serous fluid (*Figure 4*). With time, the hyperreflective material pools inferiorly within a pocket of serous retinal detachment. FA may reveal early blockage and late staining but, in many cases, FA is unremarkable (41-43). Indocyanine green angiography (ICGA) may reveal hyperfluorescent spots corresponding to the vitelliform lesions (44). FAF reveals areas of hyperautofluorescence corresponding to the vitelliform material clinically and on OCT (*Figure 4*). The clinical features may closely resemble a bestrophinopathy and it should be noted that an idiopathic acute exudative polymorphous vitelliform maculopathy may be indistinguishable on funduscopy from the paraneoplastic variant (45).

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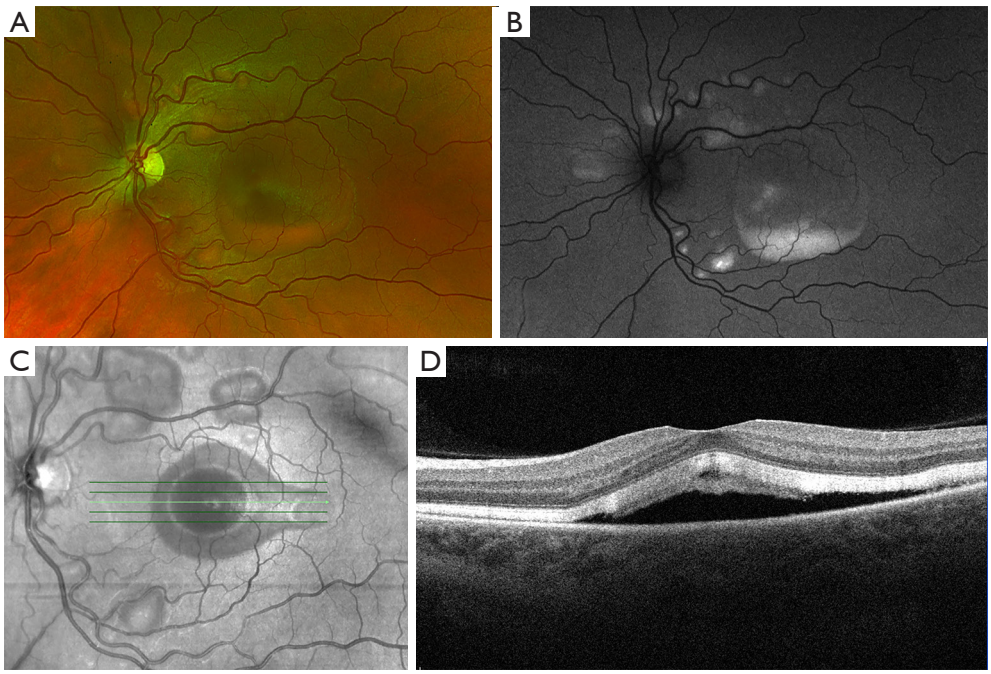

Figure 4 Multimodal imaging in the patient with paraneoplastic vitelliform maculopathy. Pseudocolor photo (A) shows multiple yellowish vitelliform lesions in the posterior fundus with are hyperautofluorescent (B). Near infrared imaging (C) highlights some of the vitelliform lesions and the optical coherence tomography horizontal line scan (D) shows subretinal hyperreflective material as well as hyporeflective subretinal fluid.

The pathophysiology of PVM is unclear but mechanistically it would seem that there is a soluble factor produced either by the primary tumor or by the immune system in response to the tumor which impacts RPE cell function (6). Several different circulating anti-retinal and anti-RPE antibodies have been described in patients with PVM but none appear to be uniformly present in all such patients (6). Treatment involves management of the underlying malignancy. Mueller *et al.* reported on a case of a patient who presented with PVM 1 month following the diagnosis of metastatic melanoma (43). The metastatic disease was treated with immunotherapy, radiosurgery and radiation over a 48-month period and interestingly the maculopathy was noted to improve or worsen in parallel with the metastatic disease burden.

Conclusions

The paraneoplastic retinopathies are a heterogeneous group of conditions with overlapping clinical features and pathophysiology. Establishing a diagnosis can be very challenging and is reliant on multimodal retinal structural and functional testing and clinical suspicion. Early diagnosis may however lead to improved chances of survival in cases where the diagnosis of an underlying malignancy has not yet been discovered. Novel insights into disease pathophysiology may allow for more targeted therapeutics and additional research on this topic is warranted.

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