Ocular Paraneoplastic Syndromes: A Critical Review of Diffuse Uveal Melanocytic Proliferation and Autoimmune Retinopathy

Thomas A. Weppelmann, MD, PhD, MPH[1], Sabrina Khalil, MD[1], Nabeel Zafrullah, MD[1], Sabah Amir, MD, MBA[1], and Curtis E. Margo, MD, MPH[1,2] 📶

Abstract

Background: Dozens of paraneoplastic syndromes affect the visual system ranging from conjunctival pemphigoid to encephalopathy of the occipital cortex. The most profiled ocular syndromes are bilateral diffuse uveal melanocytic proliferation (BDUMP) and the autoimmune retinopathies.

Purpose: To review the critical features of these 2 entities then concentrate on advancements in treatment made within the last 10 years.

Study Design: Literature review with structured data abstraction.

Results: Major insights into pathogenesis have been wanting. Plasmapheresis appears to improve vision in a substantial proportion of patients with BDUMP. The number of clinical variables that influence visual outcome in paraneoplastic retinopathies combined with the variety of local and systemic treatment options makes interpretation of clinical effectiveness difficult.

Conclusions: The rarity of these disorders makes randomized clinical trials unlikely. It may be time for a clinical professional organization to use a modified Delphi method to establish a consensus algorithm for the diagnosis and management of retinal paraneoplastic syndromes to augment clinical communications and clinical trials.

Introduction

Paraneoplastic syndrome refers to a remote, non-metastatic effect of cancer. Dozens of ocular syndromes have now been causally linked to remote cancers, most of which were recognized within the last 70 years. The renowned French internist Armand Trousseau (1801-1867) was the first person to describe a paraneoplastic syndrome in 1865.[1] His observation that *phlegmasia alba*, or painful white inflammation of the extremities, with progressive cachexia was due to an underlying cancer predated any insight into the mechanism(s) of the remote effect. Trousseau considered the association causal because the painful inflammations, now attributed to venous thromboses, occurred too often in persons dying of cancer to be coincidental.

The wide range of paraneoplastic syndromes currently known to exist mostly fall into 2 general categories: those that mediate their remote effects through peptides, proteins, prostaglandins and hormones, and those through immunoglobulins. These are

[1]Departments of Ophthalmology, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
[2]Departments of Pathology and Molecular Biology, Morsani College of Medicine, University of South Florida, Tampa, FL, USA

Corresponding Author:
Curtis E. Margo, MD, MPH, Departments of Ophthalmology, Morsani College of Medicine, University of South Florida, 13330 USF Laurel Dr, Morsani Building 4th Floor Dermatopathology, Tampa, FL 33612, USA.
Email: cmargo@usf.edu

not necessarily mutually exclusive pathways. Aberrant peptides or proteins produced by cancers, for instance, could induce antibodies, which through molecular mimicry target host tissues. A third group remains unknown or unclassifiable.

This paper presents an update and critical review on the 2 most profiled ocular paraneoplastic syndromes: bilateral diffuse uveal melanocytic proliferation (BDUMP) and cancer-associated retinopathy (CAR), including the latter's subset melanoma-associated retinopathy (MAR). These syndromes present challenges with diagnostic and medical management as visual symptoms can precede the diagnosis of cancer by months to years, while substantially adversely impacting quality of life.

Methods

Literature search was conducted through PubMed using terms 'BDUMP' 'cancer-associated retinopathy', 'melanoma-associated retinopathy', 'ocular paraneoplastic syndrome', and 'autoimmune retinopathy'. Information extraction was limited to English language and peer-reviewed papers. Retrieved articles revealed several systematic reviews through 2016. This permitted a more concentrated literature search over the last 10 years. The bibliographies of articles found in the literature were examined for relevant material. Clinical and laboratory findings on cases reported since 2012 were abstracted by 4 authors (TW, SK, NZ, SA) and then critically reviewed by all authors.

Bilateral Diffuse Uveal Melanocytic Proliferation

In 1982, Barr and associates reported 4 patients with a peculiar bilateral proliferation of uveal melanocytes that resembled bilateral uveal melanomas without any evidence of systemic spread.[2] In each case, the bilateral proliferation was temporally associated with a non-ocular systemic malignancy. The clinical findings were so striking that it seemed unlikely such a disorder could have been previously overlooked. The authors uncovered a similar case reported in the German literature 16 years earlier, but otherwise the entity appeared novel.[3] The 1966 paper described 'flachenhaften' or flat, geographic, and extensive uveal melanomas in enucleated eyes from a patient who subsequently died of a large retroperitoneal cancer.[3] Barr and associates suggested the name BDUMP and arrived at 4 essential clinical features: (1) simultaneous occurrence of bilateral diffuse involvement of the uveal tracts, (2) a preponderantly benign appearing cytological makeup of the melanocytic tumors, (3) no evidence of metastasis from the melanocytic tumors, and (4) the presence of an associated systemic malignant neoplasm proved by biopsy or autopsy. They concluded that these lesions represented a new syndrome where melanocytes of the uveal tract proliferated in response to a systemic malignant neoplasm.

The syndrome was further characterized by Gass et al.[4] in 1990 to include vision loss accompanied by 5 cardinal ocular signs: (1) multiple, round, or oval, subtle, red patches at the level of the retinal pigment epithelium (RPE) in the posterior fundus; (2) a striking pattern of multifocal areas of early hyper-fluorescence on fluorescein angiography corresponding to these patches; (3) development of multiple, slightly elevated pigmented and nonpigmented uveal melanocytic tumors as well as evidence of diffuse thickening of the uveal tract; (4) exudative retinal detachment; and (5) rapid progression of cataracts. The classic ocular fundus pattern described by Gass has been referred to as leopard spots because of its reticulated color configuration (so-called giraffe pattern). The reticulated pattern of depigmentation is not diagnostic of BDUMP and has been described in metastatic cancer, leukemic infiltration of the choroid, and lymphoma, all of which can occur bilaterally. A less common pattern found in BDUMP is characterized by multiple pigmented nodules without leopard spots (Figure 1).

Since that time, approximately 100 cases have been reported in the literature and several comprehensive reviews of the subject have been published, including in depth descriptions of clinical findings.[5-7] Most patients were diagnosed with BDUMP between the sixth and seventh decade of life and had a variety of non-ocular cancers. A majority of malignancies in women have arisen in the urogenital tract (over 73%), while in men, lung tumors are most common (58%).[6,8] The primary non-ocular malignancy is known to exist in roughly half of patients who develop BDUMP, while in the remaining cases it is occult at the time of ocular diagnosis.[6] The average survival after diagnosis of BDUMP is just over 15 months with a range from 10 months to 5 years.[6] These figures should be interpreted within the context that the majority of cases reported in the literature do not provide long-term follow-up. The visual prognosis of BDUMP is poor with most patients suffering progressive bilateral visual loss usually attributed to a combination of exudative retinal detachments and cataract formation.[5-7] Protracted detachment of the macula will also result in secondary photoreceptor degeneration, another cause of subnormal vision whose individual contribution is difficult to estimate.

Pathogenesis

The observation that about a quarter of patients with BDUMP develop pigmentation of skin or mucous membranes suggested to early investigators a shared pathogenesis with acanthosis nigricans.[5] Acanthosis nigricans, however, is a cutaneous manifestation of several groups of unrelated disorders, of which only 1 is neoplastic.[9] The molecular pathway of acanthosis nigricans is mediated through a variety of growth factors, including insulin growth factor receptor 1, epidermal growth factor receptors, and fibroblast growth factors.[10] Although abnormal growth factors have not been identified in BDUMP, the search for a humoral promoter of melanocyte proliferation is ongoing.

Miles and associates demonstrated that a factor in the serum and plasma from patients with BDUMP could stimulate the growth of cultured melanocytes.[11] They further characterized the substance as existing within the IgG fraction of serum and plasma samples. Because the substance caused
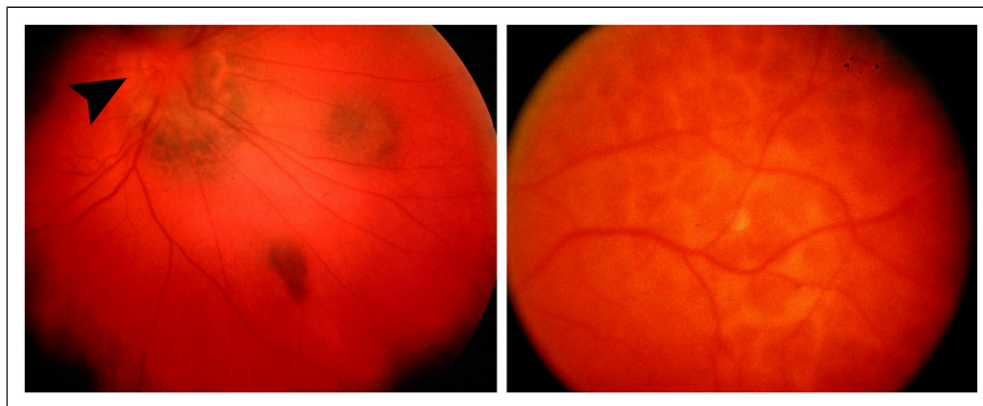
Figure 1. Ocular fundus from 2 different patients with bilateral diffuse uveal melanocytic proliferation (BDUMP), both confirmed histologically. The photograph on the left shows a congested disc (arrowhead) surrounded by an elevated pigmented tumor. Two separate pigmented nodules are present at 3 and 5 o'clock. The right panel is from another patient showing the reticulated (giraffe) pattern highly characteristic of BDUMP.

cultured melanocytes to elongate and proliferate, it was named CMEP factor.[11] Supportive indirect evidence of CMEP factor came from Jansen and associates who showed that incubated plasma from 2 patients with BDUMP resulted in a statistically significant increase in number of melanocytes before plasmapheresis but not after.[12] These findings provided sufficient justification to recommend plasmapheresis for the vision-threatening complications of BDUMP.[13] CMEP factor, however, was not be found in the IgG-enriched plasma from another patient with BDUMP who failed treatment with plasmapheresis.[14]

Gene analysis was found in 3 available case reports. Two patients had no chromosomal abnormalities in 3, 6, and 8, although 1 displayed trisomy 5 by single nucleotide polymorphism analysis.[6,15] Mittle and colleagues reported a patient with polysomy 8q with normal chromosome 3 and no mutations of *GNAQ/GNA11*.[16] Chromosomal aberrations are common in uveal melanoma, with loss of chromosome 3 and polysomy 8q associated with metastasis. The 2 patients with no abnormalities in 3 and 8 argue against melanoma, while polysomy 8q found in a third patient is consistent with the possibility of frank malignancy. The absence of *GNAQ and GNA11,* two mutually exclusive driver mutations in uveal melanoma, support paraneoplastic syndrome.

Bilateral diffuse uveal melanocytic proliferation has also been reported as a complication of immune-modulating therapy.[17] The meaning of such an association is difficult to interpret since the patient had advanced renal cell carcinoma and the development of BDUMP could have been related to the underlying malignancy.

## Unilateral Diffuse Uveal Melanocytic Proliferation (UDUMP)

Five reports of possible UDUMP have appeared in the literature, none of which were verify histologically.[18-22] Clinical follow-up when available was brief, averaging less than 6 months (Table, supplement). Since ocular sequential development of BDUMP is known to occur, the lack of sufficient clinical follow up raises concern that sequential or asymmetric ocular involvement had not been excluded. One case reported simultaneous unilateral intraocular lymphoma and UDUMP without histopathologic examination.[18] Cases of UDUMP need to be interpreted cautiously.

Pathology

The histopathology of BDUMP generates more questions than answers to the discussion of pathogenesis. Most tumors are composed of modestly plump spindle melanocytes, but a substantial number are admixed with epithelioid melanocytes. The original paper reporting BDUMP described 3 of the 4 cases as having tumors with a mixture of "more malignant-appearing epithelioid cells."[2] The authors had difficulty objectively calling these tumors benign nevi and illustrated their dilemma with several high-magnified photomicrographs consistent with melanoma, albeit minor components. Others have confirmed that mitotic and Ki-67 indices are lower than that encountered in uveal melanomas and metastases have not been reported.[6] The spindle shaped melanocytes with occasional exception are not the delicate bipolar cells seen in uveal nevi.[5] Local invasion and necrosis are common. The bulky, thick tumors found in many eyes also do not correspond to the gross morphology of uveal nevi, which rarely are more than 3 mm thick. The examples shown in this paper illustrate these points. Both are well-documented cases of BDUMP (Figures 2 and 3). When they have been shown to experienced ocular pathologists as unknown unilateral eye tumors, the diagnosis of mixed cell type melanoma has been offered without hesitation. The diagnoses, however, were amended to BDUMP when the clinical history of bilateral involvement with non-ocular cancer was provided.
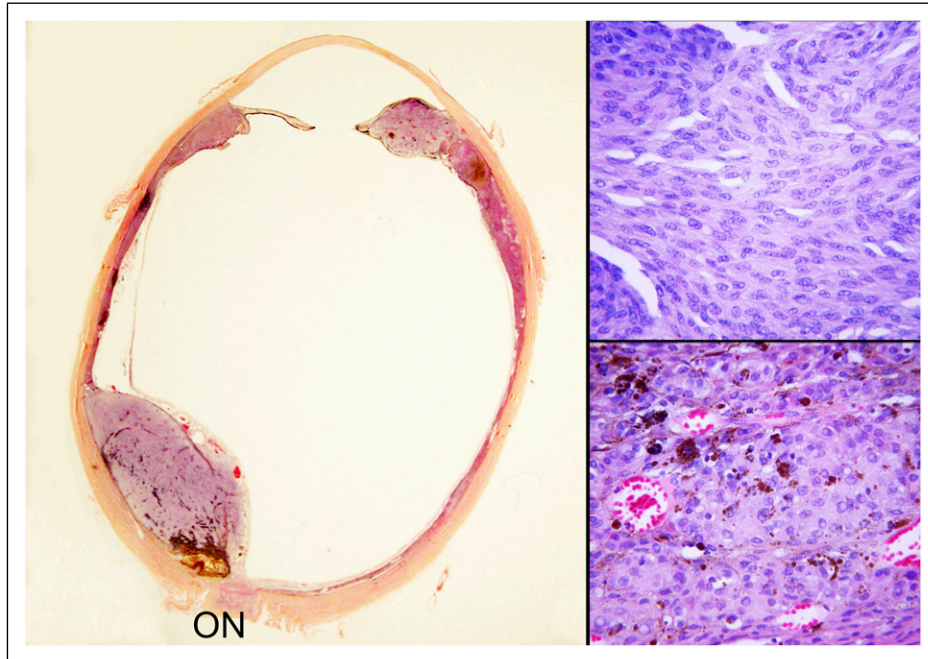
Figure 2. Enucleated eye with BDUMP with focal dome-shaped tumors up to 5 mm thick. Areas of focal necrosis were present. The tumor was composed on plump spindle cells with discernible nucleoli (upper right). The abundance of cytoplasm is some melanocytes was consistent with epithelioid cells.
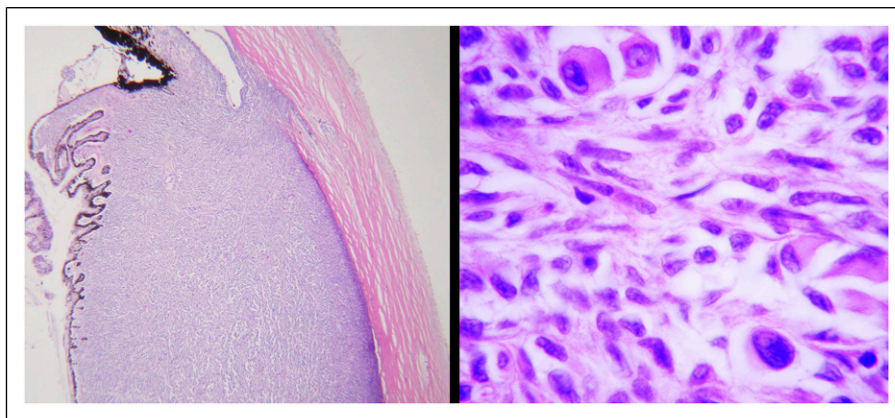
Figure 3. Another patient with BDUMP showing effacement of ciliary body by melanocytes that range from spindle-shaped to epithelioid. Many melanocytic nuclei have angulated shapes and vary in size. This degree of cellular pleomorphism is beyond the morphologic spectrum of uveal nevus.

Are the melanocytes of BDUMP an expression of uveal melanocytic hyperplasia? Unlike the RPE, uveal melanocytes typically display little response to noxious injury. The so-called hyperplastic pigmented scars associated with age-related macular degeneration, toxoplasmosis, focal laser burns, etc. are due to the proliferation of RPE with a minor contribution from uveal melanocytes. Unlike uveal nevi and reactive hyperplasia, lesions of BDUMP are bulky, irregular masses. They contain areas that can be indistinguishable cytologically from melanoma, have foci of necrosis, and invade adjacent tissues. From a purely morphologic vantage point, the findings in BDUMP are unique and not easily pigeonholed into benign nevus or reactive hyperplasia.

Therapy

Moreno and associates provided a thorough review of treatment of BDUMP through 2016.[8] Their findings were based on 68 cases found in the literature and focused on visual acuity or visual function as the primary outcome. Nine of the 68 patients

received treatment for the non-ocular cancer without ocular-directed therapy. Five of these 9 showed visual improvement. Visual recovery can be substantial in some patients when cataract removal is indicated and possible. Most patients received local or systemic corticosteroids, alone or in combination with other therapies like radiation or intravitreal injection of anti-VEGF medications. These therapies failed to display any clear evidence of effectiveness. Mets and associates used plasmapheresis 3 times per week in a patient with BDUMP in 2011.[23] They reported improvement in visual acuity from 20/40 and 20/50 to 20/20 and 20/25 in the right and left eye, respectively. However, vision declined after plasmapheresis was stopped. Through 2017, ten cases treated with plasmapheresis were found in the literature. Six showed some improvement in vision.[12,24-30] After 2017, 40 new cases of BDUMP were recorded in the literature of which 10 received plasmapheresis (Table, supplement). Vision in 7 of these cases was reported to have benefited.

Although the humoral agent responsible for BDUMP remains unknown, plasmapheresis with concurrent treatment of the non-ocular malignancy has shown the greatest promise in treating visual complications. Since some cases of BDUMP have been associated with anti-retinal antibodies, the use of local or systemic corticosteroids may be beneficial in select situations.[31]
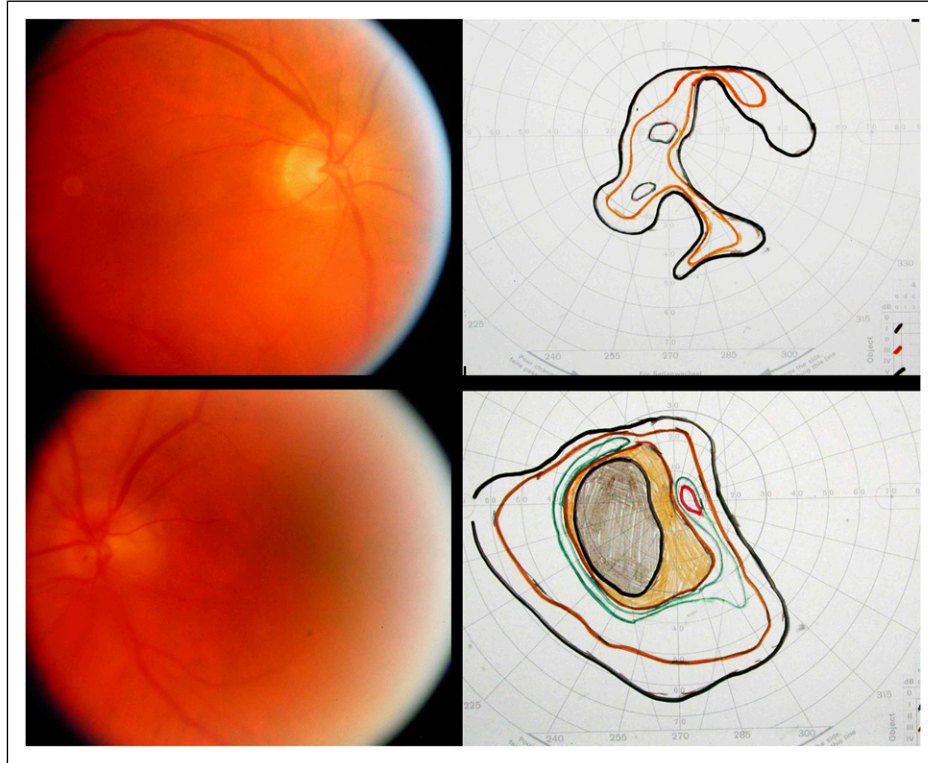
Cancer-Associated Retinopathy

In 1976, Sawyer and associates described 3 patients with pathologically confirmed photoreceptor degeneration, which they attributed to a remote effect of cancer.[32] The patients were all women who had onset of vision loss prior to their cancer diagnoses, nearly absent electroretinograms (ERGs) (an indirect measure of mass retinal function), and ring scotomas on visual field testing. The hypothesis that these findings were due to a paraneoplastic syndrome was based on the exclusion of known macular diseases, select destruction of photoreceptors, and the temporal relationship to cancer diagnoses. By 1982, another research group detected anti-retinal antibodies in patients with outer retinal degeneration and small cell carcinoma of the lung.[33] They proposed that the process was an autoimmune disorder. Within the decade, researchers at University of California at Davis reported antibodies to the retina and optic nerve and thus named the condition CAR.[34,35] Recoverin, a 23-kDa calcium-binding protein in photoreceptors, was the first antigen discovered to be the target of CAR antibodies.[36] Since the identification of recoverin, numerous other antigens have been implicated including tubby-like protein, heat shock cognate protein 70, aryl hydrocarbon receptor interactive protein-like 1, interphotoreceptor retinoid binding protein, photoreceptor cell-specific nuclear receptors, and retinal enolase, to name a few.[37,38] As many as 50% of CAR patients studied have high titers of autoantibodies other than recoverin. In addition to photoreceptors, immune-mediated injury to bipolar cells and RPE have also been implicated. Some patients with CAR have demonstrated more than 1 autoantibody and a proportion of antigens that are not specific to the retina (eg, enolase).

One anti-retinal antibody found to be associated with CAR is anti-TRPM1, which has also been found in MAR. MAR was first described in 1988 by Berson and Lessel.[39,40] Early investigators suspected non-photoreceptor retinal injury based on ERG findings. In 2011, researchers identified an antibody to TRPM1, a protein found in ON bipolar cells. In a 2011 study, the antibody was identified in 2 of 26 patients with MAR and in 1 patient with CAR.[41] The sensitivity of anti-TRPM1 as a marker for MAR thus came into question. Other investigators found that one-third of patients with cutaneous melanoma and no visual symptoms had anti TRPM1 antibodies, raising additional questions of specificity.[42] The MAR syndrome differs from CAR in several respects other than primary malignancy. Patients tend to be younger, latency between onset of visual symptoms and cancer diagnosis is longer, and the ERG shows preservation of a-wave.[43-64] The latter finding was the clue that either the bipolar cell or Muller cell rather than photoreceptor was the site of immunologic injury. A number of other anti-retinal antibodies have been identified in patients with MAR, including 35-kDa Muller glial cell protein, 22 kDa neuronal antigen, 135-kDa, 46-kDa, 94-kDa, 30- kDa, 33-kDa, 35-kDa, 23-kDa, and 30-kDa.[43-64] Since the ERG finding of a preserved a-wave is non-specific and auto-antibodies other than anti-TRPM1 lack specificity, the minimal case-defining features of MAR remain unclear.

Researchers from the Casey Eye Institute wanted to determine whether the type of anti-retinal antibody found in patients with CAR conferred any specificity to a non-ocular malignancy.[64] They confirmed 12 different anti-retinal antibodies that demonstrated tendencies to associate with some underlying cancers. For example, anti-arrestin antibody was associated with cutaneous melanoma, and anti-aldolase antibody was associated with colon cancer. However, the overall specificity was poor, and the authors concluded that antibody screening had little role as a CAR biomarker.[64] The specificity of anti-retinal antibodies in general has been questioned. Several studies have shown that anti-retinal antibodies can be found in roughly a third of healthy individuals.[65-67] Others have found poor concordance in laboratory testing amongst patients with possible CAR and a lack of laboratory standardization.[68,69] A study out of the Mayo Clinic has thrown the clinical utility of antibody testing in presumed autoimmune retinopathy into question. The investigators found that 13 of 14 persons without evidence of immune retinopathy (both normal controls and those without cancer diagnoses) tested positive for anti-retinal antibodies.[70] Among those positive, a median of 5 anti-retinal antibodies was found.

The search for a unifying cellular or molecular pathogenesis of CAR and related immune-mediated retinal cancer syndromes continues. While generally thought of as autoimmune retinopathy in which tumor-related antigens cross react with the retina, CAR confounds that interpretation by the

Figure 4. Cancer associated retinopathy in a man with severe bilateral vision loss. Retinal examination was considered normal. A cataract in the left eye makes the photograph in the lower left appear hazy. Kinetic visual fields maps (Goldmann perimetry) show a C-shaped island of vision in the right eye (upper right) and a constricted field in the left eye (lower right). The colored lines represent plots of threshold light sensitivities (isopters) with the outer isopters corresponding to brighter and larger light targets. The patient's vision rapidly declined a month before the diagnosis of small cell lung cancer. The eyes showed profound photoreceptor degeneration without inflammation at autopsy.

large number of implicated antibodies suggesting that some may represent an epiphenomenon.[71] The epiphenomenon hypothesis views the primary injury to retina (eg, autoantibody, noxious protein, etc.) as releasing additional retinal antigens and thereby induces the formation of secondary antibodies. Antibodies in this situation would not be considered as having a primary role in pathogenesis. The prevalence of anti-retinal antibodies among normal individuals and those without retinopathy adds further confusion to the discussion. Immunologic injury to retina in CAR is unusual in that the retina is an immune privileged tissue protected by the blood-retinal barrier, suggesting that other inciting factors exist. Many of the antibodies associated with CAR other than recoverin are not specific to the retina. To date, most research into pathogenesis has focused on autoantibodies to recoverin and α-enolase, and their ability to induce apoptosis of retinal cells.[72,73]

Clinical

Patients with CAR and MAR present with painless progressive visual loss with little in the way of retinal findings (Figure 4). Late stages may display mild pigment mottling, vascular attenuation, and disc pallor. Visual fields often reveal ring scotomas and optical coherence tomography shows outer

retinal thinning with loss of the inner-outer photoreceptor junction (also called the ellipsoid zone). A flat ERG confirms outer retinal injury in CAR. The ERG in MAR tends to show preservation of a-waves. The differential diagnosis of paraneoplastic retinopathy included toxic and metabolic retinopathies, retinal dystrophy, and autoimmune retinopathy *not* associated with an underlying cancer.

Pathology

The morphologic findings have provided limited insight into pathogenesis since most eyes studied represent late stages of degenerations with profound loss of outer retina (Figure 5, left panel) Figure 3. Retinal pigment epithelial changes range from non-detectable to considerable patchy degeneration with pigment migration. Some degree of either primary atrophy of inner retina or trans-synaptic degeneration is also evident. The relative lack of inflammation and necrosis is consistent with pathologic apoptosis (Figure 5).

Therapy

Results of treatment for CAR, MAR and other cancer-related paraneoplastic retinal conditions like cancer-related cone
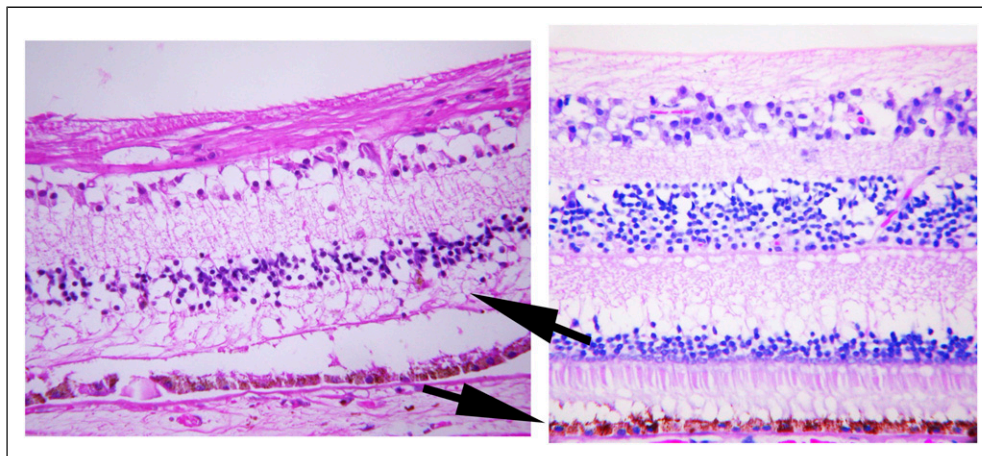
Figure 5. Macular changes in cancer-associated retinopathy roughly 2 mm from foveal center (left panel). There is nearly total absence of photoreceptors. A normal macula from same location at same magnification is seen on the right for comparison. The upper arrow points to absence of outer nuclear layer (photoreceptor nuclei) in CAR retina. The lower arrow points to corresponding retinal pigment epithelium in the normal retina, highlighting the absence of outer retina. There also appears to be a relative loss of nuclei in the ganglion cell and inner nuclear layers.

dysfunction have been mixed, and efficacy of any regimen is difficult to judge. The interpretation of short- and long-term visual outcomes is limited by small numbers, lack of standardization both in treatment protocols and outcome measures, and the variable degree of vision loss present at the initiation of treatment. These issues are further complicated by several confounding factors. One important confounder is whether the putative antigens injured by the autoantibody impact outcome or not. There is also concern over publication bias that favors encouraging results over failure.

The non-ocular malignancies in most patients with CAR-type syndromes are treated according to cancer-specific protocols, which is assumed to impact visual results by reducing tumor-producing antigens. Ethically, this assumption can never be tested in a controlled manner. One patient with CAR with Hodgkin's lymphoma had complete resolution of ocular symptoms with chemotherapy.[74] That said, reports on visual function usually found progressive deterioration in most patients despite treatment of primary malignancy supplemented with local and systemic corticosteroids.[75-80] This prompted explorations of other therapies including high-dose intravenous corticosteroids, corticosteroids plus immunomodulating agents, systemic azathioprine, systemic cyclosporine, systemic mycophenolate, plasmapheresis, intravenous immunoglobulins, and several different monoclonal antibodies (eg, alemtuzumab, rituximab, etc.). The results have been mixed in terms of short-term outcomes.[71,81-105] Since 2012, there have been 40 cases reported with extractable information (Table, supplement). Among those patients, 25 (62.5%) had more than 3 months of follow-up. Nine reported stable vision, 13 had some improvement in vision and three worsened (Table, supplement). The therapeutic benefits that have been reported with rituximab are tempered by other reports of negative effects with immune-modulating therapies.[86,99,101] Several reports have appeared in 2022 describing considerable worsening or rapid progression of immune-mediated retinopathy after initiation of immune-modulating therapy.[102-105] These apparent visual complications of therapy either mimic CAR or are a distinct complication of immune-modulating therapy. Still, others have reported benefit from treatment with intravitreal corticosteroids administered by injection or slow-release insert.[58,106] The results of small series and individual case reports are difficult to interpret or compare because many if not most patients had escalating or overlapping therapies, multiple concurrent therapies, and different putative pathogenic antibodies. The quality of documented visual outcomes also varies.

The assessment of visual outcomes in patients with MAR is even more challenging than CAR because fewer cases have been reported, no uniform diagnostic criteria exist, clinical follow-up duration is often short, and documentation of visual outcomes is frequently lacking. Since 2012, there have been 17 cases of MAR reported in the English literature (Table, supplement).[43-45,49-64] Nine of those cases reported anti-retinal antibodies, but anti-TRPM1 was present in only 2. Nine of the 17 patients had sufficient documentation to assess visual outcomes clinically. Although all patients received some form of therapy for the cutaneous melanoma, only 7 had vision-specific therapy. Four of these consisted of different forms of corticosteroids, and 2 consisted of cataract removal. Of the 9 patients with reported vision-related follow-up, 8 demonstrated an improvement in baseline vision, and 1 had stable vision.[43-64]

Summary and Conclusion

The morphology of BDUMP defies characterization using conventional terms like nevus or reactive hyperplasia. The profound effect that the proliferation of uveal melanocytes has

on ocular hemostasis (eg, exudative retinal detachment, rapidly advancing cataracts, etc.) is unlike any benign neoplasm or reactive melanocytic process known in ophthalmic pathology. The observations that a growth factor exists within the immunoglobulin fraction of plasma remains to be replicated. Plasmapheresis appears to improve vision in a substantial proportion of patients, implemented with select adjuvant therapies.

Meaningful insights into the cancer-associated retinopathies, including MAR, have been hampered by gaps in knowledge. Do anti-retinal antibodies play a primary role in pathogenesis, or are they a secondary phenomenon? Do differences in putative retinal antigens or the type of non-ocular cancer influence prognosis? These questions and others are confounded by a lack of laboratory standardization for testing for anti-retinal antibodies and the frequency that anti-retinal antibodies are found in control samples. Given the relative rarity of cancer-associated retinopathy and the variety of therapeutic options to treat vision loss, it seems that the time is appropriate for a clinical professional society to use a modified Delphi method to establish a diagnostic and management algorithm.[107] Such an algorithm could enhance communication and interpretation of clinical outcomes and be of value in future clinical trials.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Statement

No personal patient-related information is contained in this review. Our Institutional Review Board exempts literature reviews.

ORCID iD

Curtis E. Margo ⓘ https://orcid.org/0000-0003-1852-5369

Supplemental Material

Supplemental material for this article is available online.

References

1. Stolinsky DC. Paraneoplastic syndromes. *West J Med*. 1980;132:189-208.

2. Barr CC, Zimmerman LE, Curtin VT, Font RL. Bilateral diffuse melanocytic uveal tumors associated with systemic malignant neoplasms. A recently recognized syndrome. *Arch Ophthalmol*. 1982;100(2):249-255. doi:10.1001/archopht.1982.01030030251003

3. Machemer R. Zur pathogenese des flachenhaften malignen melanoms. *Klin Monatsbl Augenheilkd*. 1966;149:641-652.

4. Gass JDM, Gieser RG, Wilkinson CP, Beahm DE, Pautler SE. Bilateral diffuse uveal melanocytic proliferation in patients with occult carcinoma. *Arch Ophthalmol*. 1990;108(4):527–533. doi:10.1001/archopht.1990.01070060075053

5. O'Neal KD, Butnor KJ, Perkinson KR, Proia AD. Bilateral diffuse uveal melanocytic proliferation associated with pancreatic carcinoma: A case report and literature review of this paraneoplastic syndrome. *Surv Ophthalmol*. 2003;48(6):613-625. doi:10.1016/j.survophthal.2003.08.005

6. Klemp K, Kiilgaard JF, Heegaard S, Nørgaard T, Andersen MK, Prause JU. Bilateral diffuse uveal melanocytic proliferation: Case report and literature review. *Avta Ophthalmol* 2017;95(5):439-445.

7. Parakh S, Maheshwari S, Das S, et al. Presumed diffuse uveal melanocytic proliferation. A case report and review of the literature. *Am J Ophthalmol Case Rep* 2022;13(27):01582. doi:10.1016/j.ajoc.2022.101582

8. Moreno TA, Patel SN. Comprehensive review of treatments for bilateral diffuse uveal melanocytic proliferation: A focus on plasmaphereis. *Int Ophthalmol Clin*. 2017;57(1):177-194. doi:10.1097/IIO.0000000000000156

9. Das A, Datta D, Kassir M, et al. Acanthosis nigricans: A review. *J Cosmet Dermatol*. 2020;19(8):1857-1865. doi:10.1111/jocd.13544

10. Hu Y, Zhu Y, Lian N, Chen M, Bartke A, Yuan R. Metabolic syndrome and skin disease. *Front Endocrinol*. 2019;10:788. doi:10.3389/fendo.2019.00788

11. Miles SL, Niles RM, Pittock S, et al. A factor found in the IgG fraction of serum of patients with paraneoplastic bilateral diffuse uveal melanocytic proliferation causes proliferation of cultured human melanocytes. *Retina*. 2012;32(9):1959-1966. doi:10.1097/IAE.0b013e3182618bab

12. Jansen JC, Van Calster J, Pulido JS, et al. Early diagnosis and successful treatment of paraneoplastic melanocytic proliferation. *Br J Ophthalmol*. 2015;99(7):943-948. doi:10.1136/bjophthalmol-2014-305893

13. Graham BC, Pulido JS, Winters JL. Seeing is believing: A review of apheresis therapy in the treatment of ophthalmologic disease. *J Clin Apher*. 2018;33(3):380-392. doi:10.1002/jca.21607

14. Lavine JA, Ramos MS, Wolk AM, et al. Heterogeneity of cultured melanocyte elongation and proliferation factor in bilateral diffuse uveal melanocytic proliferation. *Exp Eye Res*. 2019;184:30-37. doi:10.1016/j.exer.2019.04.006

15. Rahimy E, Coffee RE, McCannel TA. Bilateral diffuse uveal melanocytic proliferation as a precursor to multiple systemic malignancies. *Semin Ophthalmol* 2013;30(3):206-209. doi:10.3109/08820538.2013.835835

16. Mittal R, Cherepanoff S, Thornton S, Kalirai H, Damato B, Coupland SE. Bilateral diffuse uveal melanocytic proliferation: Molecular genetic analysis of a case and review of the literature. *Ocul Oncol Pathol*. 2016;2(2):94-99. doi:10.1159/000440766

17. Góngora LM, Santalla C, Toledo DC, Díaz Vico T, Esteban E. Bilateral diffuse uveal melanocytic proliferation (BDUMP) as ocular toxicity from durvalumab in advanced renal cell carcinoma. *Eur J Cancer*. 2022:171:10-17. doi:10.1016/j.ejca.2022.04.037

18. Campos Polo R, Garcia Guisado D, Rubio Sanchez C, Bueno García P, Márquez Ivacevich NT. Lymphoma and unilateral diffuse uveal melanocytic proliferation when both conditions co-exist in the eye. *Arch Soc Esp Oftalmol*;2020: 95(2):98-102.

19. Menezes C, Carvalho R, Neves-Martins J, Teixeira C. Bilateral diffuse uveal melanocytic proliferation presenting as a giant unilateral choroidal nevus. A case report. *Ocular Oncol Pathol*. 2016;2(1):54-58.

20. Reddy S, Finger P. Unilateral uveal melanocytic proliferation. *Br J Ophthalmol* 2007;91(12):1726-1727.

21. Spaide RF. Unilateral diffuse uveal melanocytic proliferation. *Retin Cases Brief Rep* 2018;12(4):263-265. doi:10.1097/ICB.0000000000000519

22. Ayachit G, Ayachit A, Joshi S, Vasudevan SV. A rare case of unilateral diffuse melanocytic proliferation. *Indian J Ophthalmol*. 2018;66(4):588-590. doi:10.4103/ijo.IJO_979_17

23. Mets RB, Golchet P, Adamus G, et al. Bilateral diffuse uveal melanocytic proliferation with a positive ophthalmoscopic and visual response to plasmapheresis. *Arch Ophthalmol*. 2011;129(9):1235–1238. doi:10.1001/archophthalmol.2011.277

24. Navajas EV, Simpson ER, Krema H, et al. Cancer-associated nummular loss of RPE: Expanding the clinical spectrum of bilateral diffuse uveal melanocytic proliferation. *Ophthalmic Surg Laser Imag*. 2011;42:e103–e106. doi:10.3928/15428877-20111020-02

25. Jaben EA, Pulido JS, Pittock S, Markovic S, Winters JL. et al. The potential role of plasma exchange as a treatment for bilateral diffuse uveal melanocytic proliferation: A report of two cases. *J Clin Apher*. 2011;26:356–361. doi:10.1002/jca.20310

26. Alasil T, Coady PA, Koudsi S, Mathur M, Materin MA. Bilateral diffuse uveal melanocytic proliferation: A case report. *Retin Cases Brief Rep*. 2017;11(1):71-74. doi:10.1097/ICB.0000000000000292

27. Niffenegger JH, Soltero A, Niffenegger JS, Yang S, Adamus G. Prevalence of hepatocyte growth factor and autoantibodies to α-HGF as a new etiology for bilateral diffuse uveal melanocytic proliferation masquerading as neovascular age-related macular degeneration. *J Clin Exp Ophthalmol*. 2018;9(4):1–7. doi:10.4172/2155-9570.1000740

28. Schelvergem KV, Wirix M, Nijs I, Leys A. Bilateral diffuse uveal melanocytic proliferation with good clinical response to plasmapheresis and treatment of the primary tumor. *Retin Cases Brief Rep*. 2015;9(2):106–108. doi:10.1097/ICB.0000000000000104

29. Alrashidi S, Aziz AA, Krema H. Bilateral diffuse uveal melanocytic proliferation: A management dilemma. *BMJ Case Rep*. 2014;2014:bcr2014204387. doi:10.1136/bcr-2014-204387

30. Pulido JS, Flotte TJ, Raja H, et al. Dermal and conjunctival melanocytic proliferations in diffuse uveal melanocytic proliferation. *Eye*. 2013;27(9):1058–1062. doi:10.1038/eye.2013.131

31. Saito W, Kase S, Yoshida K, et al. Bilateral diffuse uveal melanocytic proliferation in a patient with cancer-associated retinopathy. *Am J Ophthalmol*. 2005;140(5):942–945. doi:10.1016/j.ajo.2005.05.048

32. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF. Blindness caused by photoreceptor degeneration as a remote effect of cancer. *Am J Ophthalmol*. 1976;81(5):606-613. doi:10.1016/0002-9394(76)90125-2

33. Korngluth SE, Klein R, Appen R, Choate J. Occurrence of anti-retinal ganglion cell antibodies in patients with small cell carcinoma of the lung. *Cancer*. 1982;50(7):1289-1293. doi:10.1002/1097-0142(19821001)50:7<1289::aid-cncr2820500711>3.0.co;2-9

34. Thirkill CE, Roth AM, Keltner JL. Cancer-associated retinopathy. *Arch Ophthalmol*. 1987;105(3);372-375. doi:10.1001/archopht.1987.01060030092033.

35. Thirkill CE, Fitzgerald P, Sergott RC, Roth AM, Tyler NK, Keltner JL. Cancer-associated retinopathy (CAR syndrome) with antibodies reacting with retinal, optic-nerve, and cancer cells. *N Engl J Med*. 1989;321(23):1589-1594. doi:10.1056/NEJM198912073212307

36. Polans AS, Burton MD, Haley TL, Crabb JW, Palczewski K. et al. Recoverin, but not visinin, is an autoantigen in the human retina identified with a cancer-associated retinopathy. *Invest Ophthalmol Vis Sci*. 1993;34(1):81-90.

37. Przezdzieck-Dolyk J, Brzecka A, Ejma A, et al. Ocular paraneoplastic syndromes. *Biomedicines*. 2020;8(11):490. doi:10.3390/biomedicines8110490

38. Dutta Majumder P, Marchese A, Pichi F, Garg I, Agarwal A. An update on autoimmune retinopathy. *Indian J Ophthalmol*. 2020;68(9):1829-1837. doi:10.4103/ijo.IJO_786_20

39. Kordyś M, Przeździecka-Dołyk J, Turno-Kręcicka A, Misiuk-Hojło M. Immunopathogenesis of ophthalmological paraneoplastic syndromes; recent findings. *Adv Clin Exp Med*. 2018;27(10):1431-1439. doi:10.17219/acem/73860

40. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. *Am J Ophthalmol*. 1988;106:307-311. doi:10.1016/0002-9394(88)90366-2

41. Kondo M, Sanuki R, Ueno S, et al. Identification of autoantibodies against TRPM1 in paraneoplastic retinopathy associated with ON bipolar cell dysfunction. *PLoS One* 2011;6(5): e19911. doi:10.1371/journal.pone.0019911

42. Duvoisin RM, Ren G, Haley TI, Taylor MH, Morgans CW. TRPM1 autoantibodies in melanoma patients without self-reported visual symptoms. *Invest Ophthalmol Vis Sci*. 2019; 60:2330-2335. doi:10.1167/iovs.19-26775

43. Poujade L, Samara Q, Mura F, Guillot B, Meunier I, Du-Thanh A. Melanoma-associated retinopathy during prembrolizumab treatment probably controlled by intravitreal injections of dexamethasone. *Doc Ophthalmol*. 2021;142(2)257-263. doi:10.1007/s10633-020-09795-8

44. Tian JJ, Coupland S, Karanjia R, Sadun AA. Melanoma-associated retinopathy 28 years after diagnosis. *JAMA Ophthalmol.* 2017; 135(11):1276-1277. doi:10.1001/jamaophthalmol.2017.3500

45. Elsheikh S, Gurney SP, Burdon MA. Melanoma-associated retinopathy. *Clin Exper Dermtol.* 2020;45(2):147-152. doi:10.1111/ced.14095

46. Haus AH, Palmowski AM, Pfohler CE, et al. Melanoma-associated retinopathy: Screening for melanoma associated retinopathy in patients with cutaneous malignant melanoma. *Neuro Ophthalmol.* 2002;27:121–137. doi:10.1076/noph.27.1.121.14294

47. Ladewig G, Reinhold U, Thirkill CE, Kerber A, Tilgen W, Pfohler C. Incidence of antiretinal antibodies in melanoma: Screening of 77 serum samples from 51 patients with American joint committee on cancer stage I-IV. *Br J Dermatol.* 2005;152: 931–938. doi:10.1111/j.1365-2133.2005.06480.x

48. Pföhler C, Haus A, Palmowski A, et al. Melanoma-associated retinopathy: High frequency of subclinical findings in patients with melanoma. *Br J Dermatol.* 2003;149:74–78. doi:10.1046/j.1365-2133.2003.05377.x

49. Elwood KF, Pulido JS, Ghafoori SD, Harper CA, Wong RW. Choroidal neovascularization and chorioretinal atrophy in a patient with melanoma-associated retinopathy after ipilimumab/nivolumab combination therapy. *Retin Cases Brief Rep.* 2021; 15(5):514-518. doi:10.1097/ICB.0000000000000882

50. Patel SR, Moysidis SN, Koulisis N, et al. Is it melanoma-associated retinopathy or drug toxicity? bilateral cystoid macular edema posing a diagnostic and therapeutic dilemma. *Am J Ophthalmol Case Rep.* 2018;10:77-80. doi:10.1016/j.ajoc.2018.01.030

51. Roberts P, Fishman GA, Joshi K, Jampol LM. Chorioretinal lesions in a case of melanoma-associated retinopathy treated with pembrolizumab. *JAMA Ophthalmol.* 2016;134(10): 1184-1188. doi:10.1001/jamaophthalmol.2016.2944

52. Shinohara Y, Mukai R, Ueno S, Akiyama H. Clinical findings of melanoma-associated retinopathy with anti-TRPM1 antibody. *Case Reports Ophthalmol Med.* 2021;2021:6607441. doi:10.1155/2021/6607441

53. Ueno S, Inooka D, Nakanishi A, et al. Clinical course of paraneoplastic retinopathy with anti-TRPM1 autoantibody in Japanese cohort. *Retina.* 2019;39(12):2410-2418. doi:10.1097/IAE.0000000000002329

54. Evoy F, Lafortune J. First case of melanoma-associated retinopathy with conjunctival melanoma. *Can J Ophthalmol.* 2020;55(4):e153-e155. doi:10.1016/j.jcjo.2020.01.006

55. Hamdan SA, Breazzano MP, Daniels AB. Triple therapy with rituximab, IVIg and intravitreal corticosteroids for melanoma-associated retinopathy (MAR): TTRIIC does the trick. *Retin Cases Brief Rep.* 2020;16:775-778. doi:10.1097/ICB.0000000000001081

56. Abou-Samra A, Tzekov R, Yannuzzi NA, Tarabishy AB. Electroretinographic findings in melanoma-associated retinopathy treated by intravitreal dexamethasone implant. *Ophthalmic Surg Laser Imaging Retina.* 2021;52(8):454-456. doi:10.3928/23258160-20210727-09

57. Dabir S, Mangalesh S, Govindraj I, Mallipatna A, Battu R, Shetty R. Melanoma associated retinopathy: A new dimension using adaptive optics. *Oman J Ophthalmol.* 2015;8(2): 125-127. doi:10.4103/0974-620X.159273

58. Karatsai E, Robson AG, Taylor SRJ. Outcomes associated with sustained-release intraocular fluocinolone implants in a case of melanoma-associated retinopathy treated without systemic immunosuppression. *JAMA Ophthalmol.* 2019;137(5): 564-567. doi:10.1001/jamaophthalmol.2019.0284

59. Xie K, Kong C, Mehta MC. A case of melanoma-associated retinopathy, uveitis, and optic neuritis associated with pembrolizumab, managed with topical, intravitreal, and intravenous steroids. *J Vitreoretin Dis.* 2020;4(3):220-226. doi:10.1177/2474126419886154

60. Stead RE, Fox MA, Staples E, Lim CS. Delayed presentation of melanoma-associated retinopathy and subsequent resolution with cytoreduction surgery. *Doc Ophthalmol.* 2013;127(2): 165-171. doi:10.1007/s10633-013-9398-6

61. Yamamoto S, Hanaya J, Mera K, Miyata K. Recovery of visual function in patient with melanoma-associated retinopathy treated with surgical resection and interferon-beta. *Doc Ophthalmol.* 2012;124(2):143-147. doi:10.1007/s10633-012-9313-6

62. Khaddour K, Khanna S, Ansstas M, et al. Normalization of electroretinogram and symptom resolution of melanoma-associated retinopathy with negative autoantibodies after treatment with programmed death-1 (PD-1) inhibitors for metastatic melanoma. *Cancer Immunol Immunother.* 2021; 70(9):2497-2502. doi:10.1007/s00262-021-02875-x

63. Heberton M, Azher T, Council ML, Khanna S. Metastatic cutaneous melanoma presenting with melanoma-associated retinopathy. *Dermatol Surg.* 2019;45(4):606-607. doi:10.1097/DSS.0000000000001599

64. Adamus G, Champaigne R, Yang S. Occurrence of major antiretinal autoantibodies associated with paraneoplastic autoimmune retinopathy. *Clin Immunol* 2020;210: 108317. doi:10.1016/j.clin2019.108317

65. Ko AC, Brinton JP, Mahajan VB, et al. Seroreactivity against aqueous-soluble and detergent-soluble retinal proteins in posterior uveitis. *Arch Ophthalmol.* 2011;129(4):415-420. doi:10.1001/archophthalmol.2011.65

66. Zeng H-Y, Liu Q, Peng X-Y, Cao K, Jin S-S, Xu K. Detection of serum anti-retinal antibodies in the Chinese patients with presumed autoimmune retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2019;257(8):1759-1764. doi:10.1007/s00417-019-04359-2

67. Shimazaki K, Jirawuthiworavong GV, Heckenlively JR, Gordon LK. Frequency of anti-retinal antibodies in normal human serum. *J Neuro Ophthalmol.* 2008;28(1):5-11. doi:10.1097/WNO.0b013e318167549f

68. Faez S, Loewenstein J, Sobrin L. Concordance of antiretinal antibody testing results between laboratories in autoimmune retinopathy. *JAMA Ophthalmol.* 2013;131(1):113-115. doi:10.1001/jamaophthalmol.2013.574

69. Adamus G, Wilson DJ. Detection of antiretinal autoantibodies in serum by Western blotting. *JAMA Ophthalmol*. 2013; 131(10):1371. doi:10.1001/jamaophthalmol.2013.4588

70. Chen JJ, McKeon A, Greenwood TM, et al. Clinical utility of antiretinal antibody testing. *JAMA Ophthalmol*. 2021;139(6): 658-662. doi:10.1001/jamaophthalmol.2021.0651

71. Grewal DS, Fishman GA, Jampol LM. Autoimmune retinopathy and antiretinal antibodies: A review. *Retina*. 2014;34: 827-845. doi:10.1097/IAE.0000000000000119

72. Adamus G, Machnicki M, Elerding H, Sugden B, Blocker YS, Fox DA. Antibodies to cover in induced apoptosis of photoreceptor and bipolar cells in vivo. *J Autoimmun*. 1998;11: 523-533. doi:10.1006/jaut.1998.0221

73. Magrys A, Anekoda T, Ten G, Adamus G. The role of anti-alpha-enolase autoantibodies in pathogenicity of autoimmune mediated retinopathy. *J Clin Immunol*. 2007;27;181-192. doi: 10.1007/s10875-006-9065-8

74. Dedieu D, Bouayed E, Brézin AP. Hodgkin lymphoma associated retinopathy: Report of a case. Ocul Immunol Inflamm. 2021 May 13;1-3. doi: 10.1080/09273948.2021.1912360. *Ocul Immunol Inflamm* 2021; May 13:1-3. doi:10.1080/09273948.2021.1912360.

75. Ghadiri N, Yang Y, Burton BJ. Cancer-associated retinopathy in ampullary pancreatic cancer. *BMJ Case Rep*. 2019;12(11): e231444. doi:10.1136/bcr-2019-231444

76. Nakamura T, Fujisaka Y, Tamura Y, et al. Large cell neuroendocrine carcinoma of the lung with cancer-associated retinopathy. *Case Rep Oncol*. 2015;8(1):153-158. doi:10.1159/000380943

77. Hughes E, Moran S, Flitcroft I, Logan P. Thyroid malignancy presenting with visual loss: An unusual case of paraneoplastic retinopathy. *BMJ Case Rep*. 2016;2016:bcr2016216998. doi: 10.1136/bcr-2016-216998

78. Singh D, Tripathy K. Cancer associated retinopathy. In: *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2022.

79. Weleber RG, Watze RC, Shultz WT, et al. Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies. *Am J Ophthalmol* 2005;139:780-794. doi:10.1016/j.ajo.2004.12.104

80. Jacobzone C, Cochard-Marianowski C, Kupfer I, et al. Corticosteroid treatment for melanoma-associated retinopathy: Effect on visual acuity and electrophysiologic findings. *Arch Dermatol*. 2004;140:1258-1261. doi:10.1001/archderm.140.10.1258

81. Dy I, Chintapatla R, Preeshagul I, Becker D. Treatment of cancer-associated retinopathy with rituximab. *J Natl Compr Cancer Netw*. 2013;11(11):1320-1324. doi:10.6004/jnccn.2013.0156

82. Ferreyra HA, Jayasundera T, Jayasundera T, He S, Lu Y, Heckenlively JR. Management of autoimmune retinopathies with immunosuppression. *Arch Ophthalmol*. 2009;127: 390-397. doi:10.1001/archophthalmol.2009.24

83. Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin: Report of 3 cases. *Arch Ophthalmol*. 1999;117:471-477. doi:10.1001/archopht.117.4.471

84. Mahdi N, Faia LJ, Goodwin J, Nussenblatt RB, Sen HN. A case of autoimmune retinopathy associated with thyroid carcinoma. *Ocul Immunol Inflamm*. 2010;18:323-323. doi:10.3109/09273941003802379

85. Shildkrot Y, Sobrin L, Gragoudas ES. Cancer-associated retinopathy; update on pathogenesis and therapy. *Semin Ophthalmol*. 2011;26:321-328. doi:10.3109/08820538.2011.588657

86. Davoudi S, Ebrahimiadib N, Yasa C, et al. Outcomes in autoimmune retinopathy patients treated with rituximab. *Am J Ophthalmol*. 2017;180:124-132. doi:10.1016/j.ajo.2017.04.019

87. Hoogewoud F, Butori P, Blanche P, Brézin AP. Cancer-associated retinopathy preceding the diagnosis of cancer. *BMC Ophthalmol*. 2018;18(1):285. doi:10.1186/s12886-018-0948-2

88. Kamei M, Fujitomi Y, Kondo Y, et al. Cancer-associated retinopathy after surgery for breast cancer: A case report and review of the literature. *Surg Case Rep*. 2018;4(1):10. doi: 10.1186/s40792-018-0418-3

89. Carrera W, Tsamis KA, Shah R. A case of cancer-associated retinopathy with chorioretinitis and optic neuritis associated with occult small cell lung cancer. *BMC Ophthalmol*. 2019; 19(1):101. doi:10.1186/s12886-019-1103-4

90. Goldstein SM, Syed NA, Milam AH, Maguire AM, Lawton TJ, Nichols CW. Cancer-associated retinopathy. *Arch Ophthalmol*. 1999;117(12):1641-1645. doi:10.1001/archopht.117.12.1641

91. Yagyu K, Ueda T, Miyamoto A, Uenishi R, Matsushita H, Tanaka T. Cancer-associated retinopathy with neuroendocrine combined large-cell lung carcinoma and adenocarcinoma. *Intern Med Inside*. 2019;58(22):3289-3294. doi:10.2169/internalmedicine.2313-18

92. Duncan C, Zamir E, Teh J, Joon DL, Liodakis P. A blind spot in urology: Prostate cancer associated retinopathy. *Urol Case Rep*. 2019;24:100872. doi:10.1016/j.eucr.2019.100872

93. Mizobuchi K, Katagiri S, Hayashi T, et al. Unique and progressive retinal degeneration in a patient with cancer associated retinopathy. *Am J Ophthalmol Case Rep*. 2020;20:100908. doi:10.1016/j.ajoc.2020.100908

94. Keltner JL, Thirkill CE, Tyler NK, Roth AM. Management and monitoring of cancer-associated retinopathy. *Arch Ophthalmol*. 1992;110:48-53. doi:10.1001/archopht.1992.01080130050025

95. Weixler B, Oertli D, Nebiker CA. Cancer-associated retinopathy as the leading symptom in colon cancer. *Clin Case Rep*. 2015;4(2):171-176. doi:10.1002/ccr3.463

96. Igarashi N, Sawamura H, Kaburaki T, Aihara M. Cancer-associated retinopathy developing after 10 years of complete breast cancer remission. *Neuro Ophthalmol*. 2018;43(1):36-42. doi:10.1080/01658107.2018.1460761

97. Nivean M, Muttuvelu DV, Afzelius P, Berman DC. Paraneoplastic retinopathy associated with occult bladder cancer. *Indian J Ophthalmol*. 2016;64(3):248-250. doi:10.4103/0301-4738.181744

98. Myadam R, Gohar A. Testicular seminoma presenting with bilateral blindness: looking beyond the eye. *Cureus*. 2020; 12(4):e7534. doi:10.7759/cureus.7534

99. Turaka K, Kietz D, Krishnamurti L, et al. Carcinoma-associated retinopathy in a young teenager with immature teratoma of the ovary. *J AAPOS*. 2014;18(4):396-398. doi:10.1016/j.jaapos.2014.03.007

100. Roels D, Ueno S, Talianu CD, Draganova D, Kondo M, Leroy BP. Unilateral cancer-associated retinopathy: Diagnosis, serology and treatment. *Doc Ophthalmol*. 2017;135(3):233-240. doi:10.1007/s10633-017-9605-y

101. Or C, Collins DR, Merkur AB, Intravenous rituximab for the treatment of cancer-associated retinopathy. *Can J Ophthalmol*. 2013;48(2):e35-e38. doi:10.1016/j.jcjo.2012.11.010

102. Heng JS, Kim JM, Jones DK, et al. Autoimmune retinopathy with associated anti-retinal antibodies as a potential immune-related adverse event associated with immunotherapy in patients with advanced cutaneous melanoma: Case series and systematic review. *BMJ Open Ophthalmol* 2022:7(1):e000889. doi:10.1136/bmjophth-2021-000889

103. Chen Q, Feng C, Sun C, et al. Cancer-associated retinopathy after anti-programmed death 1 (PD-1) antibody for treating hepatocellular carcinoma- a case report of a Chinese patient. *Am J Ophthalmol Case Rep*. 2022:29(25);101370. doi:10.1016/ajoc.2022.101370

104. Ghoraba H, Or C, Karaca I, et al. Immunotherapy-induced retinopathy mimicking cancer associated retinopathy. *Am J Ophthalmol Case Rep*. 2022:26:101449. doi: 10.10116/j.ajoc2022.101449

105. Chauhan MZ, Mansour HA, Zafar MK, Uwaydat SH. Anti-programmed death ligand-1 induced acute vision loss in a patient with cancer-associated retinopathy. *Cureus*. 2022; 14(1):e21709. doi:10.7759/cureus.21709

106. Mudin J, Phagura RS, Lam W-S, Wu XN. Intravitreal dexamethasone implant use as first-line therapy for cancer-associated retinopathy. *BMJ Case Rep*. 2021;14(11): e245527. doi:10.1136/bcr-2021-245527

107. Austin R, Gordon LK, Heckenlively JR, et al. Consensus on the diagnosis and management of non-paraneoplastic autoimmune retinopathy using a modified delphi approach. *Am J Ophthalmol* 2016;168:183-190. doi:10.1016/j.ajo.2016.05.013