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

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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.

Keywords
autoimmune retinopathy, bilateral diffuse uveal melanocytic proliferation, cancer-associated retinopathy, melanoma-associated retinopathy

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...
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. 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. The 1966 paper described ‘flächenhaft’ or flat, geographic, and extensive uveal melanomas in enucleated eyes from a patient who subsequently died of a large retroperitoneal cancer. 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. 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 hyperfluorescence 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. 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%). 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. The average survival after diagnosis of BDUMP is just over 15 months with a range from 10 months to 5 years. 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. 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. Acanthosis nigricans, however, is a cutaneous manifestation of several groups of unrelated disorders, of which only 1 is neoplastic. 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. 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. They further characterized the substance as existing within the IgG fraction of serum and plasma samples. Because the substance caused
cultured melanocytes to elongate and proliferate, it was named CMEP factor. 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. These findings provided sufficient justification to recommend plasmapheresis for the vision-threatening complications of BDUMP. CMEP factor, however, was not found in the IgG-enriched plasma from another patient with BDUMP who failed treatment with plasmapheresis.

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. Mittle and colleagues reported a patient with polysomy 8q with normal chromosome 3 and no mutations of GNAQ/GNA11. 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. 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. 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. 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.” 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. The spindle shaped melanocytes with occasional exception are not the delicate bipolar cells seen in uveal nevi. 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.
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. 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. 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. 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. 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. 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.44 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.44 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.55-67 Others have found poor concordance in laboratory testing amongst patients with possible CAR and a lack of laboratory standardization.58,68 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. 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
large number of implicated antibodies suggesting that some may represent an epiphenomenon. The epiphenomenon hypothesis views the primary injury to retina (e.g., 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
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. That said, reports on visual function usually found progressive deterioration in most patients despite treatment of primary malignancy supplemented with local and systemic corticosteroids. 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. 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 immunomodulating therapies. Several reports have appeared in 2022 describing considerable worsening or rapid progression of immune-mediated retinopathy after initiation of immunomodulating therapy. 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. 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). 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.

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 nonocular 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 retinopathy and the variety of therapeutic options to treat

frequency that anti-retinal antibodies are found in control samples. Such an algorithm could enhance communication and interpretation of clinical outcomes and be of value in future clinical trials.

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

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Supplemental Material
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