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Review Article

Review of Autoimmune Retinopathy and Its Association with Melanoma and Other Malignancies

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Abstract

Autoimmune Retinopathy (AIR) is an immune-mediated degenerative retinal disorder affecting retinal cell function leading to progressive vision loss. This review aims to quantify documented AIR cases in the literature; and elucidate common visual symptoms, AIR and cancer diagnosis chronology and autoantibodies' role in AIR pathophysiology. A literature search extracted 58 Melanoma-Associated Retinopathy (MAR) and 76 Cancer-Associated Retinopathy (CAR) cases; CAR primarily consisted of lung, endometrial, ovarian and breast cancer. The majority of MAR cases presented with a melanoma diagnosis preceding onset of AIR symptoms, while the majority of CAR cases presented with AIR symptoms preceding the diagnosis of malignancy. MAR patients experienced nyctalopia and photopsias while CAR patients experienced vision loss, photopsias and nyctalopia. Anti-recoverin is the most well-established antibody implicated in AIR pathogenicity. However, autoantibodies to α-enolase, aldolase A and C, transducin-α, carbonic anhydrase II, arrestin, GAPDH and Transient Receptor Potential cation channel, subfamily M, member 1 (TRPM1) are also key components of retinal degeneration. AIR is likely caused by antibodies-targeting retinal antigens aberrantly expressed in cancer cells-penetrating the blood-retinal barrier and cross-reacting with retinal cell antigens, inducing retinal pathology. It may be appropriate to include AIR vision panel screening as standard of care for individuals with personal/family history or signs/symptoms of retinopathy or cancers for early detection and intervention.

Keywords: Autoimmune; Melanoma; Metastasis; Paraneoplastic; Recoverin; Retinopathy

Introduction

Autoimmune Retinopathy (AIR) is a degenerative retinal disease thought to be caused by antibodies, initially produced to target retinal antigens aberrantly expressed in cancer cells, cross-reacting with and subsequently targeting retinal cell antigens, leading to retinal pathology [1,2]. Autoimmune retinopathy is composed of two subtypes: paraneoplastic AIR and non-paraneoplastic AIR [1,3,4]. Paraneoplastic AIR consists of Melanoma-Associated Retinopathy (MAR) and Cancer-Associated Retinopathy (CAR) [5]. Diagnosis of MAR occurs in individuals with cutaneous melanoma [5]. Diagnosis of CAR is most commonly associated with Small Cell Lung Cancer (SCLC), breast cancer and gynecologic cancers [1,6].

Autoimmune retinopathy is an unusual condition and its diagnosis is multifactorial. Currently, there is no single test that will delineate its diagnosis. Clinical signs and symptoms of retinopathy include progressive vision loss, scotomas (blind spots), photopsias (flashes, floaters, shimmering lights), photophobia, nyctalopia (night blindness) and color vision disturbances [7-9]. Physical examination findings can include visual field defects, decreased visual acuity, or even unremarkable findings. On fundoscopic examination, AIR may present with retinal arteriole attenuation, optic disk pallor, diffuse retinal atrophy and Retinal Pigment Epithelium (RPE) abnormalities such as mottling and atrophy [6,7,10,11].

Multiple autoantibodies have been associated with AIR. The autoantibody with the highest association and sensitivity to AIR is the anti-recoverin antibody. Recoverin is a 23-kDa calcium-binding protein found primarily in retinal photoreceptors, but also in bipolar and ganglion cells, all of which regulate rhodopsin light and dark adaptation and are involved in the phototransduction cascade [12,13]. Other antibodies implicated in this condition are autoantibodies to transducin, arrestin, bestrophin, aldolase A, aldolase C, rhodopsin, Carbonic Anhydrase II (CAII), α-enolase, myelin basic protein, interphotoreceptor retinoid-binding protein, transient receptor potential cation channel, subfamily M, member 1 (TRPM1), tubby-like protein 1, heat shock cognate protein 70 and glyceraldehyde 3-phosphate dehydrogenase. Anti-retinal autoantibodies are not pathognomonic for AIR and cannot confirm the diagnosis of AIR despite its implication in AIR-up to 42% of healthy individuals without AIR can possess anti-retinal antibodies and up to 35% of CAR patients do not test positive for antibodies [7]. Additionally, anti-retinal antibodies have been detected in individuals with autoimmune diseases such as Bechet's disease and Systemic Lupus Erythematosus (SLE) [1].

Electroretinography plays a critical role in diagnosing AIR by measuring the electrical activity of the retina and quantifying the extent of retinal damage [14]. ERG can detect subtle retinal dysfunction, even before clinical manifestations of retinopathy occur [15]. A classic ERG finding of MAR demonstrates a normal a-wave and reduction in the b-wave amplitude [14,16]. Special Domain Optical Coherence Tomography (SDOCT) and Fundus Autofluorescence (FAF) also objectively quantify retinal damage such as photoreceptor atrophy, serving as adjunctive diagnostic tools to support the diagnosis of AIR [11,16]. In general, the diagnosis of AIR is made by a clinical presentation of visual disturbances in combination with a history of malignancy, an abnormal Electroretinography (ERG), and/or presence of retinal autoantibodies.

Methods

Search Strategy

Databases utilized for the literature search included PubMed, Towson University Cook One Search, University of Maryland - Health Sciences & Human Services Library OneSearch, Loyola Notre Dame Library Seeker, Science Direct and Medline. The literature search was conducted until February 20th, 2022. The keywords used for the search included "autoimmune retinopathy," "melanoma-associated retinopathy," "MAR," "cancer-associated retinopathy," "CAR," "paraneoplastic retinopathies," "melanoma," "breast cancer," "lung cancer," "small cell lung cancer," "cancer," "malignancy," "antibodies," "autoantibodies," "recoverin," "alpha enolase," "transducing," "rhodopsin," "carbonic anhydrase II", "myelin basic protein," "interphotoreceptor retinoid- binding protein," "TRPM1," "photopsia," "transduction," and "aberrant expression". In addition, the "related articles" tool in PubMed was utilized to gather additional articles pertaining to the topic. No publication date restrictions were implemented for the studies.

The reference pages of each article were searched for additional pertinent articles to gather more specific data on the case studies. The term "OR" was used to conduct a broad search to add similar concepts and terminologies. For example, "Autoimmune Retinopathy OR AIR" and "Cancer-associated retinopathy OR CAR" were utilized to encompass articles utilizing abbreviated forms of the topics. To further narrow the search, "AND" was utilized to chain together various terms with similar concepts that helped narrow down the articles such as "Autoimmune Retinopathy AND Melanoma." Finally, the term "NOT" was utilized during the search to exclude any articles outside of the study's focus by specifying "Autoimmune Retinopathy NOT Non-paraneoplastic autoimmune retinopathy".

Inclusion and Exclusion Criteria

Studies were included if they reported case studies on autoimmune retinopathy relating to either melanoma-associated retinopathy or cancer-associated retinopathy with accessible full text journal articles. All research study types such as case reports, systematic reviews, cohort studies and longitudinal studies were included. Studies were excluded if they reported cases of AIR without a confirmed AIR diagnosis or without associated melanoma or cancer. Editorials with insufficient information were excluded if the reported case could not be extracted from the reference page and verified.

Data Extraction

Titles and abstracts of each study were initially screened independently by three reviewers (JL, ST, MH). Four reviewers (JL, ST, MH, ST) reviewed full texts of each study for data extraction of MAR and CAR cases in the literature into a table that quantifies

and qualifies MAR and CAR cases verified by the reviewers. The extracted data for Table 1 includes the patient's type of carcinoma (melanoma, SCLC, breast cancer, or other solid tumors), total cases, number of cases with cancer diagnosis prior to visual symptoms, number of cases with cancer diagnosis after visual symptoms, common visual symptoms, number of cases with metastasis and results of diagnostic tests.

Cancer	Total cases	Number of cases with cancer diagnosis prior to visual symptoms	Number of cases with cancer diagnosis after visual symptoms	Common Visual Symptoms	Number of cases with metastasis	Electro-retinography	Presence of antibodies
Melanoma	58[3-5,15-43]	46	12	Photopsias, night blindness, vision loss, constriction, scotoma, blurred vision, photosensitivity	37	91.37%	75.86%
Merkel Cell Carcinoma	1[44]	–	1	Photopsias, vision loss, photoaversion	1	100%	0%
Small Cell Lung Cancer	32[8,44-64]	8	24	Vision loss, constriction, darkening of vision, photopsia, scotoma, night blindness, blurred vision, darkening of vision, loss of color vision, glare, vision better at night	8	84.37%	71.87%
Non-Small Cell Lung Cancer	6[59,65-68]	5	1	Vision loss, constriction, photopsias, night blindness	1	100%	71.4%
Breast Cancer	4[59,69-71]	3	1	Vision loss, photopsia, scotoma	3	75%	50%
Endometrial/ Uterine	11[44,64,72-80]	5	6	Vision loss, photopsia, loss	4		

Cancer				of color vision, night blindness, constriction, blurred vision, photosensitivity		100%	54.5%
Ovarian Cancer	4[59, 81-83]	3	1	Blurred vision, photopsia, scotoma, night blindness, darkening of vision	1	100%	100%
Cervical Cancer	3[65,84-85]	–	3	Vision loss, night blindness	–	100%	66.6%
Cancer of the Fallopian Tube	1[86]	–	1	Visual loss, loss of color vision, glare	–	100%	100%
Thymoma	2[59]	1	1	Constriction	–	100%	100%
Prostate Cancer	4[59,64,87]	2	1	Scotoma	–	100%	50%
Colon Cancer	2[88-89]	–	2	Constriction, glare, scotoma, vision better at night	–	100%	100%
Pancreatic Cancer	2[59,65]	1	1	Visual loss, scotoma	1	100%	100%
Small Bowel Cancer	1[90]	1	–	Night blindness, blurred vision	–	100%	100%
Gastric Cancer	1[59]	1	–	Constriction	–	100%	100%
Renal Cancer	1[91]	–	1	Scotoma, night blindness	–	100%	100%
Liver Cancer	1[92]	1	–	Constriction	–	100%	100%

Table 1: Melanoma-associated retinopathy and cancer-associated retinopathy reported cases [3-5,8,15-92].

Discussion

Table 1 shows 58 verified cases of MAR and 76 verified cases of CAR in which the occurrence of retinopathy before or after cancer diagnosis, common visual symptoms and presence of metastasis were identified. In the majority of the MAR cases, the initial diagnosis of melanoma was made prior to the onset of visual symptoms, while in the majority of CAR cases, onset of visual symptoms preceded cancer diagnosis. The equivocal chronology and association between diagnosis of AIR and diagnosis of

cancer opens up more questions in terms of the pathophysiology of the disease state of AIR. The most common visual symptoms in MAR patients were night blindness and photopsias. MAR patients described their photopsias as "flickering lights," "pulsating lights," "shimmering lights," "T.V. Static," and "floaters." The most common visual symptoms in CAR patients were vision loss, photopsias and night blindness. CAR patients described their photopsias as "shimmering lights," "flashes," "flickering specks," "cobweb vision," and "spotted vision." Additionally, some CAR patients experienced dimming/darkening of vision-two of whom likened their vision to "looking through sunglasses"-glare and vision improving at night. Darkening of vision, glare and vision improving at night were not observed in MAR patients. The presence of metastatic melanoma was identified in over half of MAR patients-diagnosis of MAR is often associated with discovery of metastasis [93]. Metastasis of cancer in CAR patients was identified in less than half of the cases.

It is difficult to ascertain the etiology of AIR to determine whether cancer preceding AIR caused the autoantibody formation or the autoantibody formation occurred prior to and independent of any malignancy. However, these authors speculate that regardless of AIR occurring before or after the diagnosis of a malignancy, a likely subclinical malignancy must have been present that remained undetected until advancing to further stages to manifest signs and symptoms or perturbations on labs and imaging [7,64,87].

These authors speculate that tumor cell antigens circulate in the serum and activate autoantibody formation [1,13]. Autoantibodies gain access to retinal cells due to compromise of the Blood-Retinal Barrier (BRB) and attack the retina through molecular mimicry whereby autoantibodies created against tumor antigens cross-react with retinal antigens and consequently target retinal cells [1,5,13,15]. The retina contains recoverin, aldolase, carbonic anhydrase II, transducin, rhodopsin, arrestin, bestrophin and interphotoreceptor retinoid-binding protein and TRPM1 all of which are subject to cross-reactivity with autoantibodies. The American Academy of Ophthamology shows autoantibodies against transducin, arrestin, bestrophin, aldolase A and C, rhodopsin, CAII, myelin basic protein and interphotoreceptor retinoid-binding protein are most commonly associated with MAR and autoantibodies against recoverin, alpha-enolase, tubby-like protein 1, heat shock cognate protein 70, Glyceraldehyde 3- phosphate dehydrogenase (GAPDH) and CAII are most commonly associated with CAR, which are reflected on Table 2 and 3. Tables 1, 2 and 3 include cases where antiretinal antibodies were found on serological and immunological testing. The positive rates of the commonly associated antibodies are demonstrated on Table 2 and 3 per our literature review. However, some journals showed cases positive for unidentified antibodies against retinal antigens or the data/author does not specify the antibodies these antibody findings were not included in Table 2 and 3 due to lack of data pertaining to the antiretinal antibodies. Interestingly, TRPM1 is not among the commonly associated MAR autoantibodies, however; our literature review found 6 MAR patients (10.34%) positive for autoantibodies against TRPM1, possibly indicating a nontrivial role and significance not previously appreciated which warrants further investigation in the future.

Antigen	Mechanism of Action	Location in the Body	Positivity Rates
Transducin	Anti-transducin antibody (40 kDa) primarily affects the scotopic response-the vision response under low light levels[94]	Retina-rods[94]	3.45% (2)
Arrestin	In the retina, arrestin conducts phototransduction. Retinal arrestin (S-antigen) is a major pathogenic antigen in autoimmune uveitis They were initially found in the visual phototransduction system and include two visual arrestins-arrestin-1 in rod cells and arrestin-4 in cone cells-and two non-visual arrestins-β-arrestin1 and β-arrestin 2[95]	Cytoplasm of retinal cells[95]	8.62% (5)
Bestrophin	Calcium ion-dependent chloride channel and a modulator for voltage-dependent calcium ion channels in retinal	Basolateral plasma membrane of the	1.72% (1)

	pigment epithelium cells[96,97]	retinal pigment epithelium[96]	
Aldolase A and C	A glycolytic enzyme that catalyzes the conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate in vertebrates Function of aldolase A and C in the retina is currently unknown[15]	Aldolase A (muscle and red blood cells) Aldolase C (brain and neuronal tissue)[15]	12.07% (7)
Rhodopsin	Component of transduction in the retina that activates the phototransduction cascade[98]	Retinal photoreceptor cells, pineal gland lens fiber, epithelial cells, cerebellum and cerebral cortex[98]	0%
Carbonic Anhydrase II	Carbonic anhydrase II (CAII) is a cytoplasmic enzyme that catalyzes conversion of carbon dioxide to bicarbonate and assists with control of pH levels as well as ion transport[93] Anti-Carbonic Anhydrase II autoantibodies inhibit CAII catalytic activity, decreasing intracellular pH and increasing intracellular calcium. They block the binding of CAII to Na+/H+ exchanger. Prevention of these functions leads to cell acidification[99]	Outer segments of photoreceptor cells, inner nuclear layer and ganglion cell layer[99]	5.17% (3)
Myelin Basic Protein	Myelin basic protein (MBP), an intrinsically disordered protein, controls adhesion of cytosolic surfaces of multilayered compact myelin[100] Cytokine production depends on an intact conformation of MBP[101] Disordered MBP is one of the key autoantigens involved in autoimmune neurodegeneration, especially multiple sclerosis[102]	Oligodendrocytes of CNS and Schwann cells of PNS[100]	0%
Interphotoreceptor retinoid- binding protein	Facilitates transfer of retinoids in visual cycle and transports lipids between retinal pigment epithelium and photoreceptors[103] Interphotoreceptor retinoid-binding protein is downregulated in animal models of retinal disease[103]	Outer segments of the photoreceptor layer[104]	0%

Table 2: Melanoma-associated retinopathy antigens and mechanisms of action [15,93-104].

Antigen	Mechanism of Action	Location Found in Body	Positivity Rates
Recoverin	Recoverin is a calcium binding protein expressed by photoreceptor cells that regulates rhodopsin[13] In malignant cells, recoverin is likely active in calcium signaling and cell proliferation. Recoverin is shed extracellularly by SCLC cells leading to autoantibody formation[13] Autoantibodies enter retinal cells through endocytosis and inhibit recoverin function increasing intracellular calcium levels leading to apoptosis of photoreceptor cells via calcium sensitive endonucleases and caspases[13]	Photoreceptor cells, SCLC cells[13].	44.73% (34)
Alpha-enolase	Alpha-enolase functions as a glycolytic enzyme in the cytoplasm of cells found in various tissues throughout the body[105]. Alpha-enolase also functions as a tumor suppressor through the regulation of c-myc proto-oncogene in the nucleus and as a plasminogen receptor on the cell surface[105] Autoantibodies to alpha-enolase decrease catalytic function of alpha-enolase, thereby deregulating glucose metabolism and depleting glycolytic ATP and increasing intracellular Ca[105] Elevated Ca^{+} within the cell leads to translocation of Bax protein to the mitochondria and subsequent release of cytochrome c resulting in apoptosis[105].	Cells in various tissues, including retinal cells[105] In retinal cells, alpha-enolase is found in the cell membrane of ganglion cells, Muller cells, rods and cones[105]	9.21% (7)
Tubby-like protein 1	Tubby-Like Protein 1 (TULP1) contributes to proper functioning of photoreceptor cells through transport of phototransduction proteins[99] Antibodies to TULP1 contribute to changes in photoreceptor cells and loss of photoreceptor cells[99]	Rod and cone photoreceptor cells in the retina[99]	0%

Heat shock cognate protein 70	Heat shock cognate protein 70 (Hsc70) is a molecular chaperone involved in myriad cellular functions including protection from physical and chemical damage, protein homeostasis, cell signaling, protein translocation, angiogenesis and apoptosis. Of import, Hsc70 regulates function of tumor-related genes and proteins[106,107] Hsc70 is found to be involved in the aberrant expression of recoverin in tumor cells; however, the mechanism is unknown[106]	Cytoplasm of all cells in the body[106]	1.31% (1)
Glyceraldehyde 3- phosphate dehydrogenase (GAPDH)	GAPDH is a highly conserved enzyme that catalyzes the conversion of glyceraldehyde 3-phosphate to glycerate-1, 3-biphosphate and subsequently reduces NAD+ to produce NADH[108] GAPDH plays a vital role in energy metabolism of cancer cells because GAPDH is needed in the limiting step of glycolysis[109] In cancer, high GAPDH activity increases glycolysis, thus enhancing tumor growth[109]	Cytoplasm, nucleus, plasma membrane and other intracellular organelles of cells throughout the body[109]	1.31% (1)
Carbonic Anhydrase II	CAII catalyzes the hydration of carbon dioxide (CO2) to bicarbonate (HCO3-)[93] CAII expressed on the endothelium of neovessels of cancer cells (melanoma and lung cancer for example) can induce an autoantibody formation[114]. Thus, CAII is a potential target for cancer therapy[109]	Found in most organs[114]. Human brain - oligodendrocytes, myelin and choroid plexus epithelium Endothelium of neovessels of melanoma and esophageal, renal and lung cancers[110]	3.95% (3)

Table 3: Cancer-associated retinopathy antigens and mechanisms of action [13,93,99,105-110].

Recoverin, expressed by tumor cells, initiates autoantibody formation once introduced extracellularly when tumor cells undergo cell turnover and necrosis [13]. BRB compromise is necessary for the anti-recoverin antibodies to penetrate the tight junctions of the retinal pigment epithelium [13]. The mechanism by which BRB breakdown occurs is complex and multifaceted - direct injury such as external infection, trauma and systemic diseases including diabetes and hypertension, aging-related oxidative stress and inflammation, and/or retinal neuron or glia defect/injury [111]. Each potential mechanism causes retinal inflammation and injury, ultimately damaging the RPE and tight junctions, compromising BRB integrity and disrupting the immune-privileged environment of the retina [111,112]. Once the BRB is penetrated, anti-recoverin antibodies gain access to retinal cells and activate an apoptotic mechanism of retinal cells through the cross-reactivity of retinal antigens [13]. The mechanism of retinal cell death in AIR is likely an apoptotic mechanism due to retinal histological findings of autophagosomes and macrophages in CAR and

lack of a retinal inflammatory response [13]. Anti-recoverin antibodies induce retinal cell apoptosis when binding to recoverin by amplifying rhodopsin phosphorylation, which leads to increased intracellular calcium levels and thus activation of apoptotic pathways through calcium-sensitive endonuclease and caspase [13,24]. This process culminates in the death of photoreceptors and bipolar cells, leading to visual disturbances and vision loss experienced by AIR patients.

Table 1 shows 32 cases of SCLC and 18 gynecologic cases out of 76 total CAR cases. The remainder of carcinomas associated with retinopathy include cancers of the lung, pancreas, stomach, small bowel, colon, liver, kidney, ureter, ovary, uterus, cervix, prostate and thymus. The cohort study of 209 AIR cases by Adamus was composed of breast cancer (31%), melanoma (16%), lung cancer (16%), hematological cancers (15%) such as lymphomas, leukemias and myelomas, gynecological neoplasms (9%), prostate cancer (7%) and colon cancer (6%), which are roughly reflected in our findings of verified CAR cases in Table 1, with the exception of a lower incidence of breast cancer and hematological cancers in CAR cases compared to Adamus due to the limitation of extracting and verifying individual case reports with equivocal information or unconfirmed AIR diagnosis from the literature [113]. The high prevalence of SCLC and breast cancer in CAR cases is likely due to recoverin expression by SCLC and breast cancer tumor cells. This expression initiates autoantibody formation to recoverin, which subsequently cross-reacts with recoverin antigens in retinal cells. This corroborates the findings of Maeda, et al., where recoverin was found in SCLC, lung adenocarcinoma, gastric cancer, pancreatic cancer, breast cancer, uterine cervical cancer, endometrial cancer and leukemia [114]. Interestingly, it appears recoverin is found to only be expressed, aberrantly, in cancers with associated retinopathy-both CAR and MAR-while cancers without retinopathy symptoms or AIR did not express recoverin [15,114]. Therefore, the aberrant expression of recoverin in cancers is likely the underlying etiology leading to retinopathy [114]. However, the mechanism for the aberrant expression of recoverin in cancers remains unknown. Elucidation of the mechanism behind aberrant recoverin expression in cancers can unravel the pathophysiological origin of AIR and direct potential future therapeutics. Additionally, recoverin is not found in normal adult tissue but has been found in newborn thymuses, suggesting that immunological tolerance to recoverin occurs in newborns in the setting of thymus recoverin expression [114]. Elucidation of this self-tolerance to recoverin can pave the way for novel treatment mechanisms.

Adamus found anti-α-enolase to be the most frequently detected autoantibody (30% of CAR patients), followed by autoantibodies specific to transducin (17%), CAII (14%) and recoverin (10%) [97]. Although anti-recoverin was found in only 10% of the patients, anti-recoverin was more sensitive and specific to AIR and associated cancers, particularly SCLC-nearly 100% of anti-recoverin CAR cases were diagnosed with cancer and exhibited photoreceptor degeneration [114]. On the other hand, anti-α-enolase, although more prevalent, is less sensitive and specific to AIR because anti-α-enolase was found equally associated with cancers as non-cancers [113]. Although recoverin is the most well established and highly associated antigen in the literature, other antigens such as α-enolase, transducin and CAII in CAR and rhodopsin and arrestin in MAR were also found to be aberrantly expressed and overproduced in cancers, leading to a similar retinal autoantibody mechanism as recoverin described above [113].

AIR literature notes how Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC) and lymphomas are associated with CAR. Our review of the literature revealed one case study in which the patient had a history of BCC; however, diagnosis of CAR was associated with discovery of neuroendocrine carcinoma of the fallopian tube [86]. Our literature review found no cases of CAR associated with SCC, BCC, or lymphomas.

The standard workup for vision loss involves a thorough history and physical examination supported by imaging and serologic testing [113]. The history of present illness must detail the acuity, laterality and quality of vision loss, any associated symptoms and any history of existing vision issues, trauma, or past surgeries [113]. The patient's medications should be thoroughly evaluated [113]. Physical exam should assess for any evident trauma, erythema, light sensitivity, temporal artery tenderness, proptosis and ptosis [113]. Visual acuity must be obtained in all patients, followed by assessments of the pupils, extraocular eye movements and visual fields [113]. An ophthalmoscopic examination should be utilized to evaluate the fundus for any abnormalities [113]. Diagnostic tests such as fluorescein testing, Intraocular Pressure (IOP) testing, ocular ultrasonography and Electroretinography (ERG) may be utilized to further narrow down the differential diagnosis [113]. Following a thorough history and physical exam, laboratory tests can be obtained for further workup, including Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Antinuclear Antibodies (ANA) with reflex, Complete Blood Count (CBC) with differential and

Comprehensive Metabolic Panel (CMP) [113]. Imaging such as Magnetic Resonance Imaging (MRI), Computed Tomography Angiography (CTA), or Magnetic Resonance Angiography (MRA) may be ordered if a neurological or vascular etiology is suspected [113]. If the typical workup for vision loss yields unremarkable or there is clinical suspicion for AIR given ophthalmologic signs and symptoms, then ERG is vital in assessing for AIR with antiretinal antibody testing.

Autoimmune diseases such as SLE and cancers such as breast cancer have been found to manifest autoantibodies months or years before the onset of clinical symptoms, preceding a confirmed diagnosis [96]. Similarly, though not well established, these authors speculate detection of AIR-associated autoantibodies such as antibodies to recoverin, α-enolase, aldolase A and C, transducin-α, CAII, arrestin, GAPDH and TRPM1 possess the ability to predict possible AIR or malignancies prior to clinical manifestations and diagnosis [96]. Therefore, obtaining a vision panel would be highly advantageous for anyone with unexplained vision loss to rule out AIR and possible malignancy. A vision panel to detect MAR and CAR antibodies including anti-recoverin, anti-α-enolase, anti-aldolase A, anti- aldolase C, anti-transducin-α, anti-CAII, anti-arrestin, anti-GAPDH and anti-TRPM1 could prognosticate the potential of malignancies and/or associated retinopathy. We recommend that AIR vision panel screening be incorporated into the standard of care for patients with personal history, family history, or signs and symptoms of retinopathy or cancers such as melanoma, SCLC, breast and gynecological cancers because of the potential for early detection of life-threatening malignancies, early treatment and intervention and improved prognosis of related malignancies. The detection of anti-retinal autoantibodies or the diagnosis of CAR or MAR without a preceding diagnosis of malignancy should necessitate a complete skin exam by dermatologists, comprehensive physical exam with lymphadenopathy and organomegaly check by their Primary Care Provider (PCP) and comprehensive oncologic workup to rule out possible malignancy. More autoantibodies can be included in the vision panel as technology and research becomes more readily available. However, further research is needed to elucidate each autoantibody's sensitivity, specificity, association to AIR and pathogenicity.

Our review is limited by the lack of or inability to retrieve detailed data on certain AIR case studies, potentially leading to some heterogeneity in the data retrieved. Journal articles reporting cases of MAR or CAR sometimes cited sources that are unsearchable or unobtainable through our databases. Additionally, certain source articles lack data regarding visual symptoms, confirmation of AIR or cancer diagnosis, and/or exact chronology of AIR and cancer diagnosis.

Conclusion

It is still unknown whether malignancy drives AIR, but it is highly suspect. The majority of AIR cases consists of individuals 50+ years of age who inherently are at higher risk for developing malignancy, making it difficult to discern correlation versus causation. Additionally, AIR case numbers are so low that there may not be statistical relevance. Therefore, we must establish an AIR registry in order to quantify the true incidence and be able to cross-reference this AIR registry against cancer registries to establish the origin of AIR and elucidate a cause and effect. In addition, we recommend all AIR patients or patients with unexplained retinopathy undergo a full skin exam by a dermatologist and a full physical exam with lymphadenopathy and organomegaly check by their PCP. Due to the paraneoplastic nature of this disease, we recommend referral to oncology for full oncologic work up. Since the discovery of a metastasis of melanoma has been associated with AIR, any dermatologic patient that has a history of melanoma should be asked in the review of systems whether or not they have experienced visual disturbances. These findings could alert the dermatologist to the possibility of impending AIR and/or metastasis, which would then initiate the appropriate referrals. In our review, we found photopsias, nyctalopia, visual fields constriction, blurred vision and vision loss are most prevalent and most concerning to elicit. Furthermore, these authors suggest obtaining a vision panel after the first signs of vision changes to rule out AIR and incorporate vision panel screening as standard of care for patients with personal history, family history, or signs and symptoms of retinopathy or cancers. The vision panel must at least include recoverin, α-enolase, aldolase A and C, transducin-α, CAII, arrestin, GAPDH and TRPM1. A vision panel has the potential to alert us in the detection of life-threatening malignancies at earlier stages, improve success rate of treatment and intervention and bolster the prognosis of related malignancies.

Conflict of Interest

The authors have no conflict of interest to declare.

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