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REVIEW ARTICLE

Paraneoplastic ocular syndrome: a pandora's box of underlying malignancies

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ABSTRACT: Paraneoplastic syndromes affecting the visual system are a group of conditions that arise in the systemic malignancy framework. In this review, we have provided a detailed and comprehensive overview of the published literature on the various ophthalmic paraneoplastic manifestations. A systematic review of many databases has been performed to identify ample literature on the paraneoplastic syndromes related to ophthalmology. We have discussed here the clinical features, pathogenesis, and treatment strategies of various ophthalmic paraneoplastic syndromes. It can be challenging to distinguish these disorders from their non-paraneoplastic counterparts and to determine the appropriate systemic assessment for the tumour responsible, to have a proper approach towards the management of the syndrome.

METHOD: We searched PubMed, Science Direct and Journal of Ophthalmology for studies published in English between 1995 and April 2020, incorporating the general search term "paraneoplastic ocular syndrome" with connecting terms relevant to subheadings—e.g. Key search terms were cancer-associated retinopathy, (CAR), melanoma-associated retinopathy, (MAR), paraneoplastic retinopathy, autoimmune retinopathy, autoimmune-related retinopathy, and optic neuropathy, (ARRON), acute zonal occult outer retinopathy, (AZOOR), paraneoplastic vitelliform maculopathy, paraneoplastic vitelliform retinopathy, bilateral diffuse uveal melanocytic proliferation, (BDUMP), paraneoplastic optic neuropathy, (PON), polyneuropathy, organomegaly, endocrinopathy, monoclona gammopathy, and skin changes syndrome (POEMS) and various other terms. References from identified studies have been reviewed and included if deemed appropriate, valid, and scientifically important. If referenced in a selected English paper, we contemplated papers in other languages too. We preferentially selected papers that have been published in the last 10 years, but we have included relevant older references.

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INTRODUCTION

Paraneoplastic syndromes are biological manifestations away from the primary site of the malignancy that function at a distance from the tumour without direct spread [1].

Many of the syndromes manifest through the production of hormones at a site away from the primary neoplasm and some are thought to include immune-mediated cross-reactivity between the tumour antigens and normal host tissue (Table 1). The prevalence rate of paraneoplastic syndromes is estimated to be around 10 percent of patients [2].

In this review, we have discussed various optic nerve based and retinal based paraneoplastic syndromes. Molecular mimicry is believed to be the underlying cause of their development. The structural homology of retina and other ocular proteins to these cancer antigens make them susceptible to immune-mediated damage. Nevertheless, recent work has shown that tumour-expressed growth factors may also lead to their development, especially bilateral diffuse uveal melanocytic proliferation (BDUMP) and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome (POEMS) [3]. Paraneoplastic syndromes (PNS) have certain distinguishing characteristics which include (a) diseased or damaged tissue from the primary neoplasm is far situated; (b) syndrome is not a consequence of primary tumour or primary tumour metastases; (c) a variable temporal relationship that exists between the onset of paraneoplastic syndrome and the diagnosis of the primary tumour and; (d) several paraneoplastic syndromes may be associated with one neoplasm type.

These PNS are frequently a presenting feature of the underlying malignancy and hence, understanding these syndromes and their temporal relationship with the primary neoplasm is of paramount importance.

The various types of PNS and their pathophysiology is as follows:

CARCINOMA ASSOCIATED RETINOPATHY (CAR)

CAR was first identified by Sawyer [4]. He defined CAR as the progressive blindness that indirectly results from an underlying malignancy. It is most commonly associated with small cell lung cancer, due to cross-reacting auto-antibodies against retinal antigens causing retinal dysfunction and retinal cell death [4]. It is also found associated with small cell carcinoma, gynaecological (ovarian, endometrial, and cervical) and breast malignancies. Less commonly may be found associated with non-small-cell lung carcinoma, thymus, prostate, thyroid, colon, bladder, and

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Table 1. Pathophysiology of ophthalmic paraneoplastic syndrome.

Autoimmune	Ectopic peptide
Cancer associated retinopathy (CAR)	Bilateral diffuse uveal melanocytes proliferation (BDUMP)
Melanoma associated retinopathy (MAR)	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome (POEMS)
Paraneoplastic vitelliform maculopathy (PVM)	
Paraneoplastic optic neuropathy (PON)	
Paraneoplastic Lambert-Eaton myasthenic syndrome (EMS)	
Thymoma associated myasthenia gravis	

Table 2. Various underlying malignancies associated with Paraneoplastic ocular syndrome.

CAR	MAR	BDUMP	PONS	PVM
Small cell lung cancer	Cutaneous melanomas	Reproductive tract in women (ovarian, uterine, or cervical cancer)	Small cell lung carcinoma	Choroidal melanoma
Non- small cell lung cancer	Choroidal melanomas	Lung carcinoma	B-cell lymphoma	Cutaneous melanoma
Gynaecologic malignancies	Ciliary body melanomas	Pancreatic carcinoma	Pancreatic glucagonoma	Breast carcinoma
Breast cancer	Intestinal melanomas	Colon carcinoma	Neuro-blastoma	Lung carcinoma
Bladder cancer	Choroidal nevi		Uterine sarcoma	Clear cell sarcoma of big toe
Prostrate cancer	Intranasal melanoma		Papillary thyroid	Lung adenocarcinoma
Pancreatic malignancy			Renal cell carcinomas	
Thyroid malignancy			Uterine sarcoma	
Thymus malignancy			Breast carcinoma	
Colon cancer			Prostate carcinoma	
Haematological malignancies			Nasopharyngeal carcinoma	
			Bronchial carcinoma	
			Non- small cell lung carcinoma	

pancreatic cancers. Haematological malignancies (leukaemia, lymphoma, myeloma) have also been linked to CAR (Table 2).

Bilateral loss of vision caused by both rod and cone dysfunction in CAR can occur over a period of months, and visual symptoms precede systemic malignancy diagnosis in 50% of the cases.

Pathogenesis

Molecular mimicry is considered as the driving force behind the pathogenic mechanism of CAR. The theory focusses on the p53 tumour suppressor gene mutation occurring in tumour cells. Tumour cells with retinal photoreceptors expressing antigenic epitopes induce an immune response that interacts with the retina, disrupting normal signal transmission.

Antibody production against Recoverin, a calcium binding protein, located in retinal photoreceptors, has been implicated in the pathogenesis of CAR. The human Recoverin gene is located on 17p13.1 in close proximity to P53 gene [5]. Tumour tissue collected from CAR patients with small-cell lung carcinoma has been previously identified with the aberrant activity of recoverin-like peptides [6]. Maeda et al. [7] reported that extraocular expression of the Recoverin is highly antigenic as well as uveogenic in a rat model, where animals were immunised with purified recoverin, leading to a rise in antibody titres, degeneration of photoreceptors, vitreous cells, perivasculitis and lesions of the retinal system. The high levels of IgG anti-recoverin in humans, penetrate the blood-retina barrier, and bind to recoverin molecules in the photoreceptor cells. The phosphorylation of the rhodopsin molecule increases the level of calcium intracellularly and activates the caspase-dependent apoptotic pathways. This finally leads to photoreceptor cell death.

Other immunogenic factors have also been found to contribute to CAR. Adamus et al. [8] recorded that only 65% of CAR patients had detectable anti-retinal serum autoantibodies that were not always directed against a well-characterised antigen when present. Recoverin antibodies were present in only 10% of those patients . Numerous other anti-retinal autoantibodies are associated with CAR, (as depicted in Table 3) making it immunologically heterogeneous.

Clinical presentation

The mean age of presentation of patients with CAR is 65 years with no sex predilection. Visual loss precedes the malignancy diagnosis and is chronic and progressive. Glare, photopsia, photosensitivity, reduced central vision, decreased colour perception are the presenting features of cone-related compromise. There may be defective dark adaptation, nyctalopia, annular scotoma, or other peripheral visual field loss in case of rod dysfunction. Cancer-associated cone dysfunction, which is a lesser-known variant of CAR, only affects cones in a characteristic way [6].

Fundus examination may reveal attenuated retinal arterioles, optic disc pallor, and retinal pigment epithelial (RPE) attenuation and mottling. Mild vitritis with anterior uveitis, or retinal vasculitis with or without cystoid macular oedema (CMO) may be seen (Fig. 1).

The ERG shows global retinal dysfunction, with severely decreased scotopic and photopic responses [4]. The reduction in

Table 3. Retinal autoantigens as biomarkers for subtypes of CAR.

Antibody	Target tissue	Clinical feature	Association with cancer
Anti-recoverin	Severe loss of the rod and cone system	Rapid progression to blindness panretinal degeneration extinguished ERG	~100%
Anti-enolase	Isolated cone dysfunction ganglion cell loss	Less severe vision loss Optic atrophy	~40%
Anti-transducin-a	Primary rod degeneration	Mildly progressive vision loss	~25%
Other anti-retinal autoantibodies			
Arrestin (48-kDa), carbonic anhydrase II (CAII, 30-kDa), interphotoreceptor retinoid-binding protein (IRBP, 145- kDa), heat shock cognate protein 70 (hsc-70, 70-kDa) photoreceptor cell, specific nuclear receptor (PNR, 41-kDa), tubby-like protein 1 (TULP1, 78-kDa)			

amplitude is usually seen in the early stage, when even the fundus findings may be normal (Fig. 2). Visual field shows generalised depression, or central, paracentral, arcuate, or ring scotomas [9] (Fig. 3). Optical coherence tomography (OCT) shows atrophy of macula, loss of the inner segment/outer segment (IS/OS) junction, and also the inner highly reflective layer. Due to increased metabolic demand, compromised RPE function is often seen as an increased autofluorescence region. Lymphocytosis and increased levels of cerebrospinal fluid (CSF) protein may also be seen.

Western blot analysis and immunofluorescent antibody assays using retinal sections may be done to establish auto-antibody reactivity to photoreceptor outer segments. A comprehensive assessment for potential malignancy is important in patients suspected of having CAR.

Management

A clinical triad consisting of photosensitivity, attenuated arteriole caliber, and ring scotomata was earlier proposed by Jacobson et al. [10] for diagnosis of CAR. According to Sobrin [11], if there is an unexplained vision loss and visual field deficits in the presence of a near-normal examination, CAR may be suspected.

The underlying malignancy should be primarily addressed. Although the visual prognosis is poor, and fast; yet long-term immunosuppression happens to be the mainstay of therapy for CAR.

Combinations of systemic corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIg) has also been found beneficial. They protect the photoreceptors. Following treatment with oral corticosteroids in conjunction with plasmapheresis, Murphy et al. [12] observed a decrease in anti-retinal antibody (60-kDa) titres from 1:2000 to 1:200 in a patient. The vision improved markedly in both the eyes.

Steroid-sparing immunomodulatory therapy (IMT) has also been considered as one of the modalities for treatment. Improvement of vision and visual fields were present in all the patients treated for CAR with IMT in the report presented by Ferreyra et al. [13]. However, the toxicity of the drugs is the major side effect.

Monoclonal antibodies are shown to have a positive result. Espandar et al. [14] published the positive use of alemtuzumab (anti-CD52, panlymphocytic marker) over an 8-year period to manage multiple episodes of CAR. In cases which were refractory to the usual treatment, with every alemtuzumab infusion there was a dramatic change in vision and visual fields. In another study [15], it was seen that in patients, not responding to prednisone or IVIg, rituximab (anti-CD20, B-cell marker) had a positive effect.

Animal models have shown efficacy of calcium antagonists in the treatment [16]. Adamus et al. [17] reported the use of Nifedipine, which blocked the entry of calcium into retinal cells of rats and prevented apoptosis. A subjective improvement was noted in few cases.

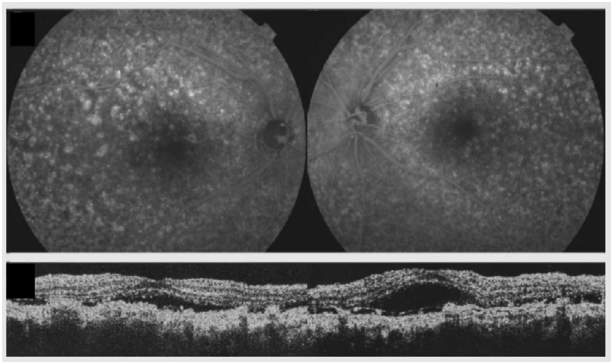

Fig. 1 A case of cancer-associated retinopathy. (**A**) Fluorescein angiography and (**B**) ICG at 1 month after symptom onset, demonstrating hyperfluorescence consistent with leakage, and hypercyanescence with dilated choroidal vessels respectively. (**C**) Fluorescein angiography at 3 min and 19 s OD and at 12 min and 3 s OS at five month follow-up demonstrating peripheral mottling and window defects. (printed with permission from 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 May 2;19(1):101).

Periocular steroid injections have shown a mixed result. Ferreyra et al. [13] reported positive outcomes with sub-tenon methylprednisolone (40–60 mg) injections in four of their CAR patients. Improvement in vision was noted.

Intravitreal corticosteroid injections may be used to improve the response of refractory CMO in cases of CAR by restoring the IS/OS junction. Huynh et al. [18] described a patient of CAR presenting not responding to any of the above discussed systemic interventions, but responded to intravitreal corticosteroid injections and stabilised the visual function.

MELANOMA-ASSOCIATED RETINOPATHY (MAR)

Berson and Lessell [19] were the first to report about MAR. This occurs due to the common neuroectodermal origin of the melanocytes and retinal cells [20]. The autoimmune reaction induces disruption and subsequent death of retinal cells, and consequent impairment of photoreceptor and signal transduction [21], and visual disturbance.

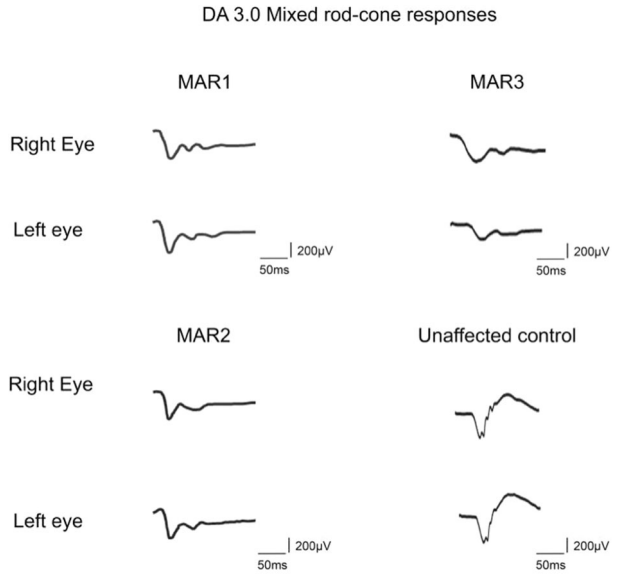

Fig. 2 ERG in a case of CAR: ISCEV- standard full-field flash electroretinography (ERG) Top traces. ERGat presentation; note severely reduced rod-specific responses, electronegative combined rod-cone response, delayed cone-specific a- & b-wave, and slightly delayed 30 Hz-flicker responses Middle traces: virtually identical ERG findings two months after presentation Bottom traces: traces from normal subject for purposes of comparison. (Printed with permission from Goetgebuer G, Kestelyn-Stevens AM, De Laey JJ, Kestelyn P, Leroy BP. Cancer-associated retinopathy (CAR) with electronegative ERG: a case report. Doc Ophthalmol. 2008 Jan;116(1):49–55).

According to Keltner et al. [22], there is a latent period of ~3.6 years between the diagnosis of the primary neoplasm and onset of MAR (Table 2).

Pathogenesis

Anti-bipolar cell antibodies guided against the depolarising or ON postsynaptic receptors interrupt neuronal signalling with related rod photoreceptors, resulting in a visual compromise mainly correlated with rods. Typically, these have been considered the distinguishing feature of MAR [23].

Antibodies to a 35-kDa Muller cell protein, a 22-kDa neuronal antigen is found both in the retina and optic nerve, and a novel 33-kDa membrane-associated protein has all been described in MAR. Transducin-a, transducin-b, arrestin, and rhodopsin auto-antibodies are also found in patients with MAR [24].

According to another hypothesis, T-cell-mediated process in the pathogenesis of MAR. According to one of the theories, cytotoxicity is the cause behind the primary attack against the retina.

In the sera of four patients with MAR targeted against the transient receptor potential cation channel, subfamily M, member 1 (TRPM1), which is expressed exclusively in retinal ON-bipolar cells, Kondo et al. [25] and Dhingra et al. [26] independently identified autoantibodies also known as melastatin 1 (MLSN1). TRPM1 has been established as the cation channel responsible for the ON-bipolar cells' light reaction [27].

Conversely, Keltner et al. [22] and Milam et al. [28] were not able to find any specific antigen. In fact, the MAR-specific antigen maybe a ganglioside, proteoglycan, lipid, carbohydrate, or a hybrid but not a protein.

Clinical presentation

Incidence is mainly seen in the 60-year of age having a male preponderance. Clinical features include sudden onset of nyctalopia and bilateral shimmering photopsia. Within a period of 4 days to 2 months symptoms become bilateral. Decreased colour discrimination has also been reported. In Keltner et al.'s [22] review, it was found that around 82% had a vision of 20/60 or better initially. The fundus examination in the initial stages is mostly normal. In later stages, retinal vessel attenuation, pallor of optic disc, and region of RPE atrophy can be seen. Vitreous cellular reaction with vasculitis and CMO may also be seen.

Visual field testing depicts generalised constriction, arcuate defects, central, or paracentral scotomas [22]. OCT shows thinning go the inner retina in the paramacular region in the later stage [29]. The ERG shows a retained dark-adapted a-wave suggesting normal photoreceptor activity accompanied by a significantly attenuated b-wave representing either bipolar cell dysfunction or synaptic transmission disturbance between photoreceptors and bipolar cells [22].

There are two confirmatory tests for MAR: Western blot or ELISA which detects the presence of serum anti-retinal antibodies from the samples taken from the patients, or retrospectively by conventional immune-histochemical staining of donor retina (especially bipolar cells) in the patients that had their eyes enucleated. It helps to detect 35- kDa Muller glial cell protein and a 22-kDa neuronal antigen are found and also antibodies against aldolase C and aldolase A (of brain origin, indicating blood-retinal barrier damage), transducin (a phototransduction protein), and mitofilin and titin.

Though anti-retinal antibodies are described in 65% of patients [30], they are seen in subjects with diabetic retinopathy and retinal vasculitis too, and sometimes in healthy controls too [31].

MAR has a triad of (i) night blindness, positive visual phenomena or visual field defects; (ii) reduction in b-wave amplitude in electroretinography (ERG); and (iii) serum autoantibodies that are reactive with retinal bipolar cells [32].

Management

Visual prognosis is guarded. Various modalities like steroid variations, plasma exchange, and IVIg have shown variable outcomes. Two procedures are mainly considered: cytoreduction (reduction of the tumour pressure and elimination of antigen stimulus) and immunotherapy (reduction of circulating autoantibodies). The cytoreductive procedure followed by systemic immunotherapy is usually the first-line treatment, with the scalp, lymph nodes, and soft tissues being the most frequent locations. Where surgery is unsuitable, cytoreductive chemotherapy or radiotherapy may be used [22]. Corticosteroid therapy in any form is seldom successful.

An analysis of 103 advanced-stage patients [33] with melanoma reported that improved prognosis is correlated with the existence of biological markers of autoimmunity, indicating that autoantibodies have a defensive part in exterminating melanoma cells, and thus reducing tumour spread with exacerbating survival. Hence, it was proposed that immunotherapy should be averted in tumour patients, even though it is being explored [34].

Immune checkpoint point inhibitors (ICIs) have shown promising results in the management of such cases. They act by suppression of inhibitory receptors to improve T-cell-mediated anti-tumour immunity and are used for advanced melanoma therapy. ICIs may also cause or intensify immune-related detrimental effects such as MAR, owing to their effect on the immune system [35]. ICIs in individuals with MAR or other autoimmune diseases should be discouraged whenever appropriate.

The benefit from local adjuvant therapy in MAR was difficult to ascertain owing to the lack of studies. Handler et al. [36] diagnosed a MAR patient with three cycles of oral alkylating chemotherapeutic temozolomide, a metastatic melanoma off-label therapy. The patient also received two concurrent, periocular triamcinolone acetonide injections of 40 mg 3 months apart. Vision bilaterally was consistent at 20/25, with visual field quality improved, with decreased scotomata size and density. This helps in considering the role of corticosteroid injections peri- or intraocularly, in cases of retinal findings.

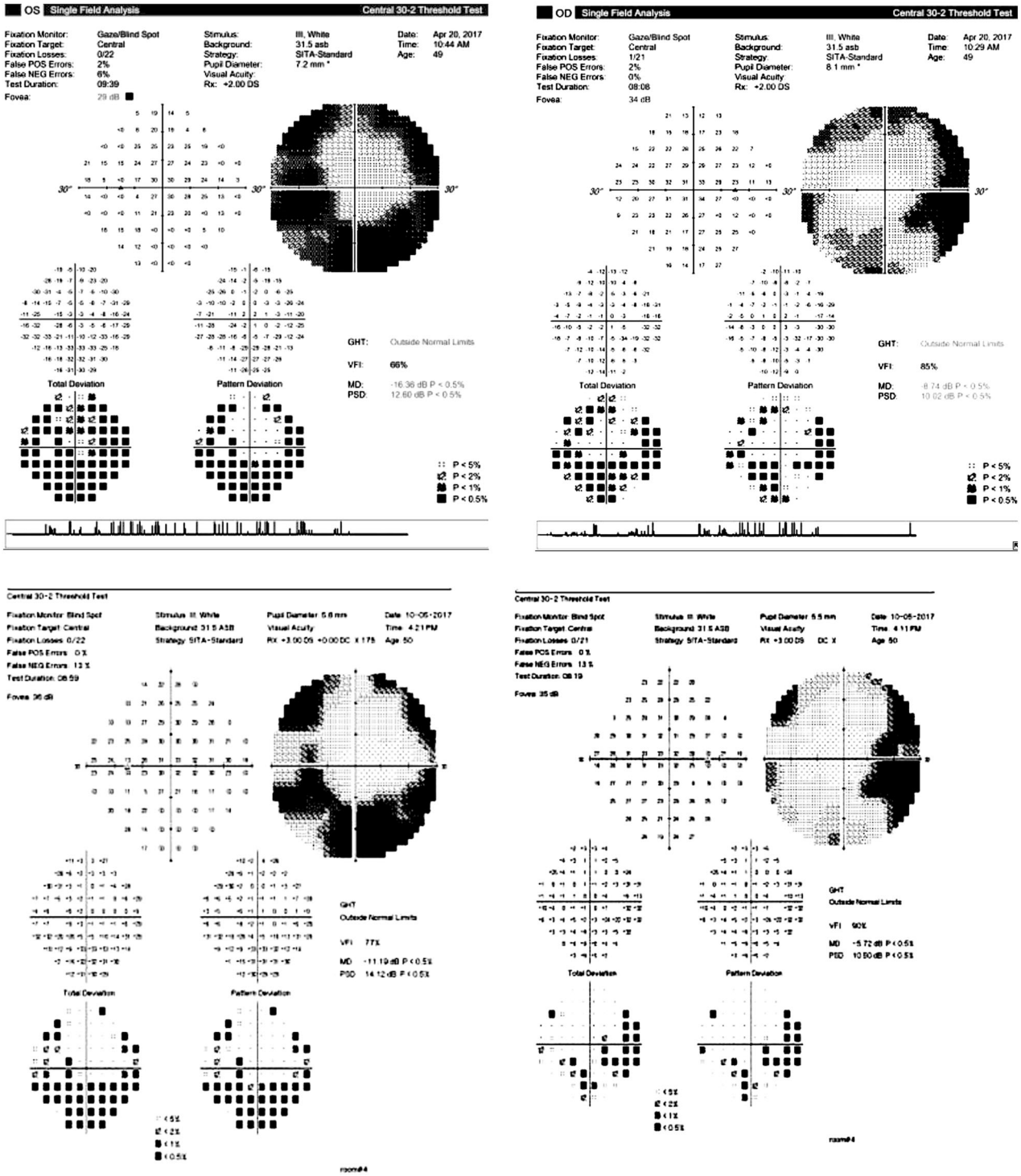

Fig. 3 Visual filed 30-2 in a case of CAR. HVF 30–2 at 2 weeks after symptom onset (above) and at sixmonth follow-up (below), with a temporal defect OD and generalised peripheral constriction OS in a patient of CAR (Printed with permission from: Carrera W, Tsamis KA, Shah R. A case of cancer-associated retinopathy with chorioretinitis and optic neuritis associated with occult small cell lung cancer. BMC Ophthalmol. 2019 May 2;19(1):101).

BILATERAL DIFFUSE UVEAL MELANOCYTIC PROLIFERATION (BDUMP)

Machemer [37] first had reported a patient with presumed pancreatic cancer in 1966, who presented with bilateral visual loss, cataracts, and retinal detachments. In 1982 Barr et al. [31] coined the term BDUMP.

Pathogenesis

Visceral malignancy triggering uveal melanoma proliferation due to molecular mimicry has been postulated as the ethology of BDUMP [38]. The initiation of uveal melanocytic proliferation in exposure to hormone-secreting visceral carcinoma, or likely coincidental occurrence of low-grade diffuse uveal melanomas

and systemic carcinoma in patients with the hereditary predisposition to neoplasia has been documented (Table 2). In addition, Miles et al. [39] have found that proliferation factor (CMEP) in serum induces the proliferation of uveal melanocytes.

Gass et al. [40] suggested that toxic or immunologic factors may be responsible for the pathogenesis of BDUMP, causing degeneration of RPE, retina, and lens. According to Chahud et al. [41], ocular hypoxia due to elevated oxidative pressure from replicating melanocytes produces a detrimental condition leading to inflammation of the RPE, retina, and lens.

Clinical presentation

Patient in the age group of 50–80 years, presents with painless vision loss which is rapid-onset, accompanied by various funduscopic findings. There is no sex predilection. BDUMP heralds systemic malignancy from months to years. Women may have underlying ovarian, uterine, or cervical cancer, whereas men may have lung, pancreatic, or colon carcinoma [42].

Gass et al.[l4] described five important characteristics for diagnosing BDUMP: (1) multifocal, round or oval, red, subretinal patches (2) hyperfluorescence pattern in early angiography phases (3) thickening of uveal tract leading to the development of slightly raised, multiple, pigmented and non-pigmented uveal melanocytic tumours, (4) exudative retinal detachment and (5) progression of cataract. There may also be angle closure due to cysts in the iris and ciliary body.

Fundus shows areas of RPE atrophy surrounded by orange areas of hypertrophied collection of RPE [43]. Window defects are seen on FA. The FFA demonstrates blocked fluorescence due to the hypertrophied RPE. OCT shows the absent RPE and presence of excrescences in IS–OS junction. B-scan ultrasonography shows choroidal thickening [44].

Management

BDUMP treatment is usually targeted to primary cancer. With the administration of systemic corticosteroids and chemotherapy, [40] although temporary improvement in the vision was described in patients with BDUMP, the majority of cases showed no effect of the corticosteroid therapy given alone and no remarkable radiotherapy effect [45].

Jaben et al. [46] and Mets et al. [47] advocated that plasmapheresis may be a promising mode of treatment, as the circulating growth factor is thought to be the cause for the various findings.

Ultimately, patients with BDUMP have poor prognosis. They have a life expectancy of a year only after diagnosis. However, plasmapheresis in adjunct may still be a viable alternative for enhancing and preserving visual function.

PARANEOPLASTIC VITELLIFORM MACULOPATHY

Many retinopathies which are supposed to be of paraneoplastic origin may present with vitelliform lesions in the fundus [48]. The diagnosis of the primary tumour in patients with a documented history of malignancy is sometimes distant from the onset of PVM. The prevalence of PVM tends to correlate with the burden of systemic disease, as all recorded cases have metastatic disease proof. In fact, PVM heralded metastatic dissemination of underlying cancers like breast carcinoma, cutaneous melanoma, clear cell tumour of lungs, etc, identified within a few months of an initial ophthalmological examination of a patient (Table 2).

Pathogenesis

Anti-retinal and anti-RPE antibodies may be present causing the typical vitelliform lesions. Koreen et al. [49] identified PRDX3 antibodies which act against a 26-kDa RPE protein. It is a mitochondrial peroxidase, protecting the oxidative damage of the cells. They proposed an autoimmune-mediated RPE epitheliopathy that culminated in the deposition of unprocessed cellular debris and probably lipofuscin, expressed through yellowish subretinal deposits at a macroscopic stage.

Eksandh et al. [50] established serum anti-RPE autoantibodies against a different 68-kDa antigen, bestrophin-1. He found it in records of patients with choroidal melanoma enucleation who had a pseudohypopyon in the residual eye with a serous macular detachment. Aronow et al. [51] found large autoantibodies titres in a PVM patient against a 30-kDa protein present in RPE and retina, known to be CAII. They also detected an unknown 35-kDa RPE protein with subtle reactivity. They inhibit CAIId catalytic activity found in the outer photoreceptor region, the inner nuclear layer, and ganglion cell layers. Hence, pH levels in the cells get decreased. There is then a subsequent increase in intracellular calcium leading to reduced cell viability in retina.

Clinical presentation

Its seen in the age group of 59 years (33–80 years) with bilateral presentation and no gender predilection [52]. The patient often presents with metamorphopsia, blurry vision, glare, shimmering photopsia, and halos. Clinically, PVM seldom presents with the stark resemblance to vitelliform retinopathies, such as the multifocal variant of Best's disease or acute exudative polymorphous vitelliform maculopathy. The fundus examination shows varying degrees of multifocal yellow-orange vitelliform lesions due to the changes at subneurosensory retina and RPE level. It is often associated with serous macular detachment [52].

The vitelliform lesions may cause blockage of background choroidal fluorescence with late staining in FFA. Some instances can display a slight early hyper-fluorescence or even dye leakage into the correct subretinal area. Corresponding fundus autofluorescence displays increased lesion fluorescence (Fig. 4).

OCT demonstrates areas of serous neurosensory detachments with dense debris over the flat RPE [52]. Serological testing shows autoantibodies against bipolar cells, rod outer segment protein (ROS, 120-kDa), bestrophin-1 (68-kDa), carbonic anhydrase II (CAII, 30- kDa), peroxiredoxin 3 (PRDX3, 26- kDa), interphotoreceptor retinoid-binding protein (IRBP, 145-kDa), and unnamed 35-kDa and 68-kDa proteins. However, ERG and electrooculography (EOG) have given inconsistent results.

Management

Regardless of the remission period, the patient should be thoroughly investigated for the systemic spread if there is any previous history of malignancy. Treatment involves variations of palliative surgical resection, radiotherapy, and chemotherapy that treat malignancy at fundamental stage. Detection of PVM has a poor prognosis, with major chunk of patients dying due to the metastasis, from months to a period of four years following diagnosis.

PARANEOPLASTIC OPTIC NEUROPATHY

Malik et al. [53] suggested an immunologic basis for PON in 1992. He identified a serum antibody reactive with neuronal and glial cytoplasm in a 63-year-old man with a subacute bilateral visual loss followed by cerebellar ataxia who subsequently was found to have a small-cell lung carcinoma (SCLC). However, other aetiologies are present too (Table 2).

Pathogenesis

Regulation of the neurogenesis is done by the Collapsin response-mediating proteins [54]. CRMP-5 subtype is seen in the normal optic nerve, adult retina, and central and peripheral neurons and also in cytoplasm of SCLC tumour cells, where cross-reaction occurs with the native tissue sites [55].

Pathologically, perivascular lymphocytic infiltration in the optic nerve is found along with axonal demyelination [55].

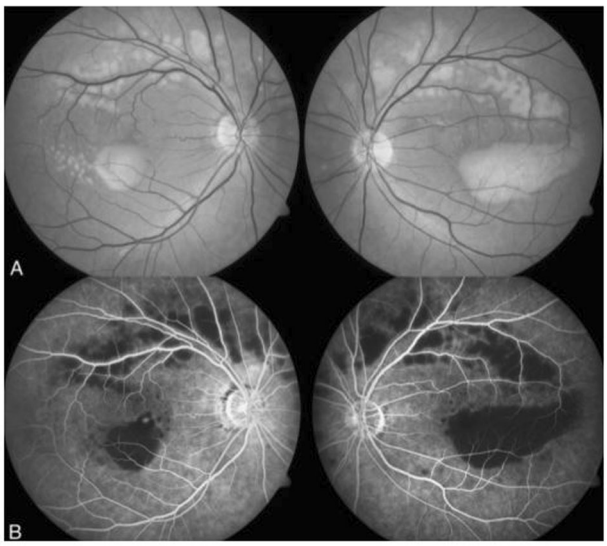

Fig. 4 Fundus photograph and FFA in a case of BDUMP. A Bilateral red-free fundus photographs show pseudofluoresence of the vitelliform lesions. **B** Bilateral fluorescein angiography images, late phase, demonstrate complete blockage of the choroidal fluorescence by the lesions. (printed with permission from Krema H, Simpson R, Altomare F, Ebadi M. Paraneoplastic Vitelliform Retinopathy In Metastatic Cutaneous Melanoma. Retin Cases Brief Rep. 2010 Summer;4(3):246–50).

Immunohistochemical studies revealed CD8þ T-cells invading the optic nerve [55].

Clinical features

Patients may complain of slowly progressive, painless, subacute, bilateral loss of vision. Mostly found in patients aged 50–75 years and typically in smokers. There may be papilloedema or optic nerve atrophy at the time of presentation. A clinical triad for the purpose of diagnosis was given by Cross et al. [55] consisting of optic neuritis, vitreous cells, and retinal vascular leakage.

Hyper-fluorescence of the optic disc corresponding to the leakage and at times peripheral retinal vascular leakage is seen in FFA. Visual fields reveal arcuate and altitudinal defects, enlarged blind spots, paracentral scotomas, peripheral constriction, or generalised depression [55]. ERG abnormalities are not generally found. However, rarely prolongation of the maximal rod-cone, cone, and 30-Hz flicker responses may be seen [55].

Neuroimaging of the brain parenchyma can show hyperintense T2 signal changes, spinal cord abnormalities, enhancement of optic nerves, or maybe unremarkable [56].

The CSF demonstrates a lymphocytic pleocytosis, oligoclonal bands, elevation of protein levels, and collapsin response-mediator protein-5 (CRMP-5) IgG titres exceeding or equalling the serum levels [57]. Antibody to the 62-kDa neuronal antigen, CRMP-5, also known as CV2 may be present [58].

PON frequently coexists with multifocal neurological dysfunction. Patients may present with ataxia, movement disorders, cognitive impairment, cranial nerve abnormalities, neuropathy, seizures, autonomic instability, or myelopathy. Neuro-ophthalmologic manifestations include vertical gaze paresis, opsoclonus, and bilateral internuclear ophthalmoplegia [55].

PON can have presentations similar to many other disorders in the age group. One must rule out the presence of neuromyelitis optica (NMO) (Devic's disease)/optic spinal multiple sclerosis (OSMS), for example by testing for anti- Aquaporin4 (AQP4) antibodies. Consider testing for anti-MOG to diagnose anti-AQP4 seronegative recurrent optic neuritis.

Management

Vitreous biopsy should be done in case of presence of CRMP-5-IgG in the serum or cerebrospinal. One may vigorously look for lung cancer. Other malignancies associated with PON should also be ruled out.

Though chances of stabilisation or even improvement of visual outcomes are there, however, in most of the patients, visual prognosis is poor. Thus, if the systemic malignancy is detected early, it may lead to a favourable outcome.

Intraocular therapy may be started in patients which will depend upon the amount of vitritis and leakage from retinal vessels.

Table 4 briefly describes the distinguishing features between paraneoplastic retinopathy and optic neuropathy.

POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL GAMMOPATHY, AND SKIN CHANGES SYNDROME (POEMS)

Bardwick et al. [59] had coined the term POEMS in 1980. It is a rare paraneoplastic disorder secondary to the dyscrasia of the plasma cell. The major findings are sclerotic bone lesions, polyradiculoneuropathy, elevated vascular endothelial growth factor (VEGF), clonal plasma cell disorder, and Castleman disease (angiofollicular lymph node hyperplasia), which may cause an asymptomatic unifocal mass to multifocal masses along with a variety of symptoms [60]. Organomegaly, characteristic skin changes, extravascular volume overload, endocrinopathy, papilledema, and thrombocytosis are the minor changes that may be found.

Pathogenesis

Patients have high levels of IL-1 b, IL-6, and TNF-a. IL- 6 and IL-1b, stimulating the VEGF production [61].

Hence, this excessive production of VEGF leads to the various pathologies found in this case. Raised serum VEGF levels cause an increase in the permeability of the vessels of the macula and optic nerve. It leads to overloading of the extravascular volume (e.g. pleural effusion, peripheral extremity oedema, pericardial effusion, ascites) [62]. Within the neurosensory retina, there is deposition of high molecular weight immunoglobulins; caused by an osmotic gradient, which leads to CMO and macular detachment [63].

High intracranial pressure (ICP), accumulation of abnormal protein substances, the involvement of cerebrospinal fluid proteins, elevated concentrations of VEGF, vasculitis, vascular occlusion, and ischemia are indicated to be implicated in ODE pathogenesis.

Clinical features

POEMS syndrome involves multiple systems. Various organs apart from the eye are targeted. It has a slight male predominance with presentation at the age of 50 years [64].

Optic Disc Oedema (ODO) [65] is the major ocular finding in this case. It is usually bilateral and is present in 29–64% of patients [64].

Patients are mostly asymptomatic. However, they may complain of blurred vision, transient obscurations of vision, and diplopia. They may even have CMO or serous macular detachment.

Visual field testing may show an enlarged blind spot, or arcuate defects, scotomata, or progressive constriction of the visual field [66]. Late optic disc leakage is seen in FFA. OCT shows CMO or macular detachment if present. Elevated VEGF levels may be seen too [67]. Increased amounts of interleukin- 6 (IL-6), tumour necrosis factor-alpha (TNF-a) and IL-1 beta (IL-1b) may also be detected [68].

Management

The underlying dyscrasia of plasma cells is targeted for successful results. Treatment includes chemotherapy of high dosage along

Table 4. Comparison of Paraneoplastic retinopathy and optic neuropathy.

	Cancer-associated retinopathy	Melanoma-associated retinopathy	Paraneoplastic optic neuropathy
Presentation	Heralds malignancy in 50% patients	Occurs in a known case of melanoma and metastatic disese o	Visual symptoms precede carcinoma
Associated malignancies	SCLC, endometrial cancer, cervical cancer, ovarian cancer, breast cancer, non-SCLC, pancreatic cancer, lymphoma, prostrate cancer, colon cancer	Melanoma, colon cancer	SCLC, renal; cell carcinoma, thyroid carcinoma
Onset	Sub-acute	Acute	Sub-acute
Age of presentation	65 years (35–87)	57.5 years (30–78)	50–75 years
Sex	No sex predilection	male to female ratio 4.7:1	No sex predilection
Symptoms	Glare, photopsias, photosensitivity, severely reduced central vision, and impaired colour perception - cone dysfunction Impaired dark adaptation, nyctalopia, ring scotoma - rod dysfunction	Nyctalopia and bilateral shimmering photopsias, decreased colour discrimination	Painless vision loss that progresses over days to weeks. Non-ocular neurological symptoms
Funds finding	Attenuated retinal arterioles, optic nerve pallor, RPE thinning and mottling. Mild vitritis with anterior uveitis, or retinal vasculitis with or without CME.	At presentation - normal Advanced stage - Retinal vessel attenuation, optic disk pallor, areas of RPE atrophy, vitreous cellular reaction with vasculitis and CME.	Optic nerve head may be normal, edematous or atrophic at time of presentation. Vitritis may be present.
Electro-physiological finding	global retinal dysfunction, severely decreased scotopic and photopic a- and b-waves	retained dark-adapted a-wave, significantly attenuated b-wave.	Not significant
CSF	Elevated protein, mild lymphocytic pleocytosis	-	lymphocytic-predominant pleocytosis, oligoclonal bands, elevated protein, and CRMP-5-IgG titers that equal or exceed serum levels
Histo-pathological finding	Degeneration of cones and rods	Ganglion cell transsynaptic atrophy, decreased bipolar neurons in inner nuclear layer, normal photoreceptors	Peri-vascular inflammation, axonal loss, demyelination of optic nerve.
Antibodies	anti-recoverin, anti-enolase, anti-transducin-a,	Anti-rod/ bipolar cells, Anti- aldolase C and aldolase A, anti-transducin, anti- mitofilin and anti-titin.	Collapsin response mediator protein - 5, anti- enolase, P/Q - type and N-type calcium channel antibody.
Antigen location	Rod, cone and ganglion cells	Bipolar cells	Optic nerve, retina, brain

with autologous stem cell transplantation, localised bone lesion radiation therapy, and systemic steroids [69].

Therapies are encouraged against increased VEGF load, though usage of intravenous bevacizumab has produced mixed results [70].

LAMBERT–EATON MYASTHENIC SYNDROME (LEMS)

LEMS has an incidence rate of 0.48 per million [71]. LEMS has a male preponderance presenting at age of 60 years. A tumour is detected in almost 50–60% of patients with LEMS [72]. SCLC, non-small-cell carcinoma, mixed lung carcinomas, prostate carcinoma, thymoma, and lymphoproliferative disorders are the associated anomalies found with LEMS.

The clinical triad of LEMS consists of weakness in the proximal muscle, autonomic symptoms, and areflexia [73]. Weakness in the proximal leg muscle followed by arms is the commonly seen initial symptom in the patient (80%) [74]. Weakness at the end reaches to oculo-bulbar region.

The ocular symptoms are seen in 0–80% of the patients, and bulbar symptoms are usually seen in 5–80% [75]. Isolated reports [76] with exclusively ocular symptoms have also been found. In comparison to MG, single muscle fatigue of the outside eye is uncommon.

In two patients during a study, [77] mild to moderate ptosis was present. No restriction in the extra-ocular movements was seen. However, slow saccades were seen in one patient and on extreme abduction, minimal diplopia in another patient was seen. Overt diplopia is rare.

Autonomic dysfunction is present in 80–96% of patients [78]. Pupillary dysfunction with abnormal its in the production of tears are seen. There was a symmetry in the ocular autonomic abnormalities. In 69% of eyes, there was an abnormality in the responses to light by the pupil. Abnormality in the reflex production of tears was found in 69% of LEMS eyes [75]. In 57% of the patients, there was a denervation hypersensitivity of both sympathetic and para-sympathetic system of the iris present. The IgG's effects on the release of acetylcholine from the terminals of the motor nerve are exercised by down-regulating presynaptic voltage-gated Ca2+ channels, possibly by cross-linking the channels with anti-Ca2+ receptor antibodies. The P/Q-type VGCC antibodies are responsible for the LEMS clinical symptoms. Such antibodies were found in 85–90 percent of LEMS patients, and some research in LEMS patients with SCLC record a figure close to 100 percent [79].

For the purpose of diagnosis, repetitive nerve stimulation (RNS) is the electrophysiological test of choice. The first compound muscle action potential (CMAP) amplitude is low in LEMS.

If LEMS symptoms are satisfactorily managed by 3, 4-diaminopyridine, then no more treatment is required. If symptoms persist, one may seek systemic treatment with prednisone and azathioprine.

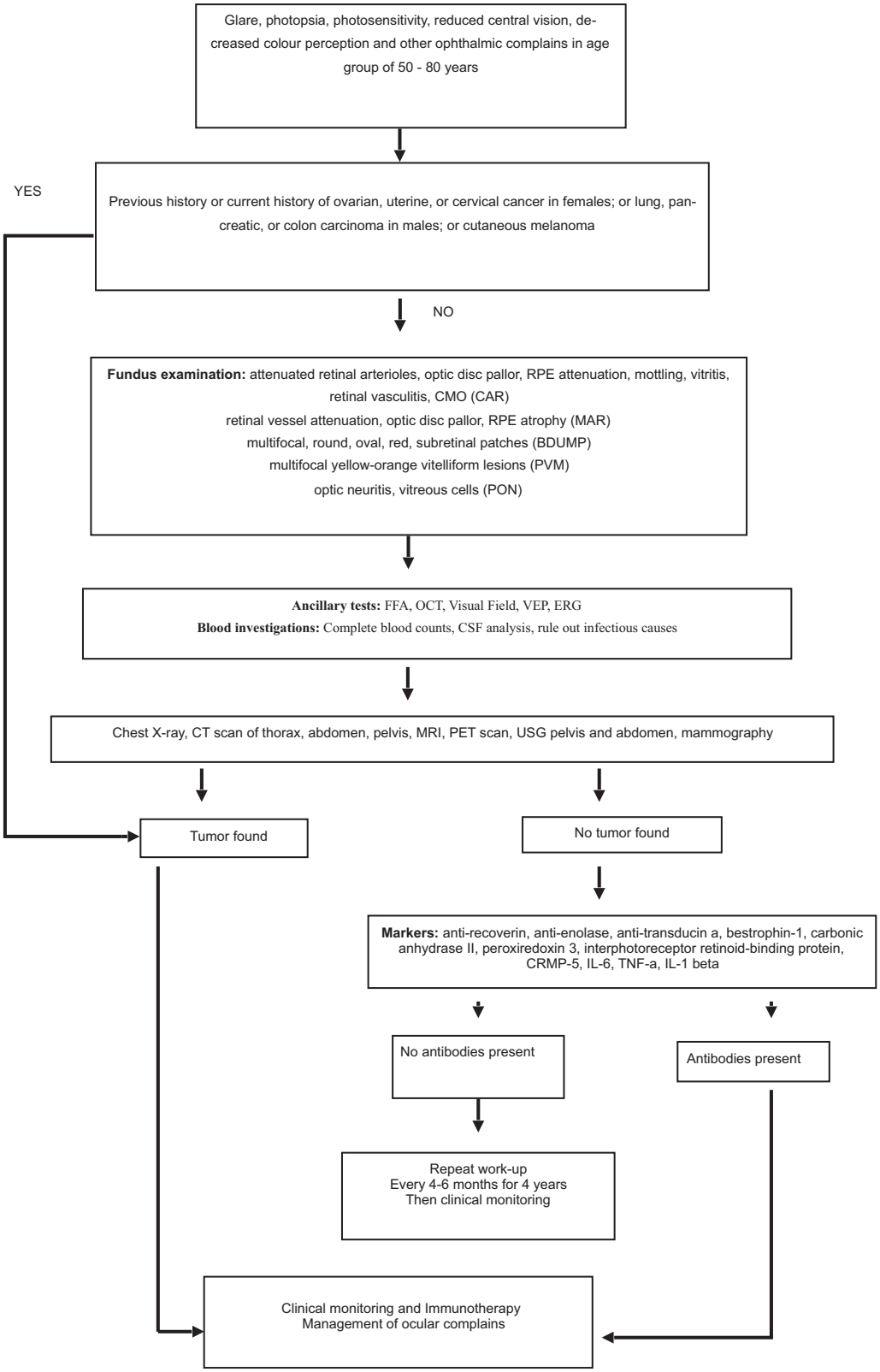

Fig. 5 Systemic evaluation in a patient with suspected malignancy. Flow chart showing management of a case of paraneoplastic syndrome.

PARANEOPLASTIC SEROPOSITIVE MYASTHENIA GRAVIS WITH THYMOMA

An autoimmune postsynaptic disease of the neuromuscular junction, distinguished by the co-occurrence of thymoma, myasthenic muscle fatigue and autoantibodies directed at the acetylcholine receptor (AChR) in 100%, and in around 75% by additional antibodies to certain components of the striated muscle cells (titin and ryanodine 1 receptor) [80]. This neoplasm's prevalence is about 10 percent of all myasthenics. The average age at the advent of thymoma-SPMG is between early and late

infancy of MG (dichotomy by age 50). Likewise, anti- Titin and anti-RyR1 antibodies are markers of a more severe course of the disorder.

Among paraneoplastic MG (thymoma), extreme weakening of the extraocular muscles is a common observation. This is explainable in terms of the multiply innervated fibres expressing embryonic (foetal) AChR in their NMJs at this site [81]. Patients may present with diurnal ptosis which worsens with the passing of day or on exertion. Expectedly, due to variable involvement of different EOMs, motility patterns are not characteristic of lesions of one or more nerves. The patient may also have unilateral eyelid retraction and orbicularis weakness. Patients with OMG may display hypometric large saccades and hypermetric small saccades, which may be a result of CNS adaptation to EOM weakness. These patients may also show intra-saccadic fatigue, a decline in the saccadic velocity during a long saccade. In most patients with OMG pupillary examination is, usually, normal. However, there are reports of fatigue of accommodation with improvement after edrophonium [82].

If in addition to anti-AChR, anti-Titin is not a finding, then consider the presence of anti-Striated muscle (unspecific) or anti-RyR1 [83]. Anti-CASPR2 (formerly called anti-vg-K-channels) is also seen. These channels are located at the neuromuscular junction and in the CNS, and Kv1.4 and are also located in the heart & smooth and striated muscles. Anti-IF alpha (interferon-alpha) (75%) and anti-Il12 (interleukin 12) are the autoantibodies that are more common in MG patients with a thymoma than in those without (75% versus 30%). Typically, the titres of these auto-antibodies increase substantially if a thymoma recurs after surgery [84]. In cases with findings other than strict myasthenic weakness, then also: anti-GAD, anti-CV2, anti-vg-Ca channel (P/Q-type) or anti-AChR (nicotinic alpha3, autonomic, ganglionic) should be evaluated.

Thymomas may be encountered up to several months or years before the onset of MG, at about the time of the MG diagnosis, and subsequently also up to several years hereafter. Therefore, a diagnosis of non-thymoma SPMG may involve frequent searches for this neoplasm at reasonable intervals, especially in cases with a later onset than before age 30.

Management

Treatment is done on the lines of MG. Immunomodulators like azathioprine along with prednisolone may be administered to the patient. Additionally, medication to improve sarcoplasmic Ca^{++}-release linked to RYR should be given. Paraneoplastic SPMG is more aggressive compared to SPMG without thymoma and often requires early and more intensive combined immunosuppressive therapy with steroids and azathioprine. A series of plasma exchanges or, alternatively, high-dose intravenous IgG to manage the MG crisis appropriately may be done.

Systemic evaluation in a patient with suspected malignancy

Existence of a clinically diagnosed paraneoplastic condition, in addition to a primary care practitioner, requires a comprehensive systematic cancer assessment. General physical inspection to be done, along with dermatological skin testing, colonoscopy, prostate screening, and/or gynaecological inspection.

Imaging studies should at least include chest X-ray and CT scan of the chest. PET may be more active than CT in identified patients believed to be seropositive for a paraneoplastic antibody [85].

More comprehensive thoracic imaging could be needed in patients where the autoantibodies are indicative for SCLC, where initial CT results are negative. The tumour usually has a small distribution and is thus more difficult to spot. Though MRI is commonly not used for primary screening in these cases. However, in the cases of PON where the initial CT scan was negative, it has been seen that MRI of the chest has helped to find out the tumour concentration [86].

In absence of any positive findings, the scans may be repeated in intervals in the future. A report issued by the task force of the European Federation of Neurologic Societies on the management of paraneoplastic neurological syndromes generally suggests repeated observations for four years every six months [87] (Fig. 5).

Diagnostic dilemmas

There are no clear diagnostic criteria for the paraneoplastic retinopathies. Rather, diagnosis is rendered by incorporating physiological characteristics, observations from tests, and outcomes from ancillary research into a clear explanation.

Alternative retinal degenerative diagnoses should also be entertained: retinitis pigmentosa; acute zonal occult outer retinopathy; non-paraneoplastic autoimmune retinopathy; toxic retinopathy (chloroquine, hydroxychloroquine, thioridazine); cone dystrophy; syphilis and vitaminosis A.

A. Acute zonal occult outer retinopathy

AZOOR was initially reported by Gass [88] in 1992. It is a retinal disease that is idiopathic in nature. There is a sectoral outer retinal dysfunction that is acute in nature and is taking place in photoreceptors [89].

It includes multiple evanescent white dot syndrome, multi-focal panuveitis and choroiditis, acute idiopathic blind spot enlargement, punctate inner choroidopathy, and acute macular neuroretinopathy. They have common clinical characteristics with AZOOR and related autoimmune mechanisms.

Table 5. Differentiating features between AZOOR and para-neoplastic retinopathies.

	AZOOR	Paraneoplastic retinopathies
Age group	35–40 years	Sixth to seventh decades
Sex	Female preponderance	No sex predilection; except MAR (male > female)
Associated history	History of antecedent viral-like illness or associated systemic autoimmune disease	No such associated history
Laterality	Unilateral	Bilateral at onset
Vision	Visual acuity is minimally affected in AZOOR	Similar to MAR; contrast to CAR
Fundus finding	Unremarkable RPE mottling Retinal vascular abnormalities rare CME rare	RPE mottling rare Retinal vascular abnormalities often seen CME seen
Electro-Physiology	ERG changes depict a more global retinal dysfunction Electronegative ERG pattern of MAR not commonly seen	Reductions in a- and b-wave amplitudes in CAR Electronegative ERG pattern of MAR
Anti-retinal antibody testing	May not be as valuable	Very valuable

Clinical features

It is found in the age group of 35–40 years with female preponderance (3.2:1 ratio over males) [90].

According to Gass, [88] AZOOR presents unilaterally and with complaints of scotoma and photopsia. Visual acuity is minimally affected (In 74% it is found to be 20/40 or better) [90]. Initially the fundus findings are normal. However, later there may be RPE mottling leading to loss of visual fields. Abnormalities of retinal vasculature and CMO are rarely seen in AZOOR [90].

Autofluorescence may show deterioration of outer retina and RPE; and SD-OCT, may show confined loss of photoreceptor layer and IS/OS complex. Gass et al. [91] noticed abnormality in the 55 eyes, both in photopic and scotopic ERG. Francis et al., [92] in the 30-Hz cone flicker response, noted a delay in the implicit time.

Testing of anti-retinal antibody does not play any significant role for AZOOR. It is hence important to distinguish AZOOR from the various paraneoplastic retinopathies (Table 5).

B. Autoimmune-related retinopathy and optic neuropathy

This entity was earlier known as steroid-responsive optic neuropathy [93]. There are a set of patients presenting with a typical profile that may hint towards the diagnosis of paraneoplastic retinopathy, but when worked up systematically, no diagnosis of malignancy is made. This group of patients is classified as ARRON, non-paraneoplastic autoimmune retinopathy, or recoverin-associated retinopathy.

Patients are usually of 50 years age, with the male: female ratio of 1:2. They may have complaints of painless loss of vision which can vary from 20/20 to no perception of light. The fundus examination reveals optic disk pallor. Most patients have CMO [13].

Antibodies have been found against the antigen which is found in optic nerve and retina ie 22-kDa, recoverin and a 35-kDa component of Muller cells [94]. Adamus et al. [95] observed antibodies against a-enolase.

Corticosteroids are usually used as first line of drugs if no systemic illness is present. In addition to this, immunotherapies can be given in combination. The case of ARRON was documented by Oyama et al. [96] in a patient who was immune to traditional therapies; and was hence given autologous hematopoietic stem cell transplantation along with the strengthening of pain, sensory acuity, and sensory fields.

Sensibly, ARRON is a diagnosis of exclusion established through systematic assessment and sometimes re-evaluation at potential times to rule out an underlying malignancy. Unexplained impairment of vision will also contribute to evidence of a paraneoplastic condition behind it.

CONCLUSION

Paraneoplastic retinopathy and optic neuropathy can be great masqueraders. The patient may not give any history of malignancy. A diligent ophthalmic examination aided by precise investigations can aid in the diagnosis of these entities. Diagnosis and management of PNS ride on localising the primary malignancy and its appropriate staging. Involving the other concerned physicians in the management will definitely help in the better prognosis of the patient. A multidisciplinary approach is required for the precise management of these syndromes so that patients can have an increased chance of survival.

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AUTHOR CONTRIBUTIONS

PS and AM were involved designing the review protocol, writing the protocol and report, screening potentially the eligible studies, extracting and analysing the data, interpreting the results and updating the reference lists. HCG, JSB, and ST were involved in creating the tables and collecting the required photographs. They also took part in writing the manuscript and also in proof-reading of the same.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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