

**OCULAR CLUES TO OCCULT MALIGNANCY: CAN VISUAL CHANGES
SERVE AS EARLY BIOMARKERS OF CANCER BEFORE CLINICAL
DETECTION?**

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Abstract

Cancer is most curable when it is smallest, yet the majority of solid tumours are still discovered only after they declare themselves through mass effect, systemic illness, or incidental imaging. The eye offers a quietly remarkable alternative: it is the only site in the body where neural tissue, its blood supply, and the microvasculature can be inspected non-invasively, in vivo, and at subcellular resolution through an ordinary dilated fundus examination. This narrative review explores how visual symptoms and ocular signs—paraneoplastic retinopathies, distant metastases to the uveal tract, neuro-ophthalmic syndromes, and so-called masquerade phenomena—may precede the clinical detection of an underlying malignancy, sometimes by months or even years. Drawing on the recent systematic review literature and major case series, we outline the mechanisms by which tumours announce themselves in the eye, the patterns that should raise suspicion of an occult primary, and the diagnostic pathway from fundus photograph to whole-body imaging. We argue that selected visual changes, particularly rapidly progressive bilateral photoreceptor dysfunction, new-onset uveal lesions in adults, and unexplained optic disc oedema, deserve recognition as potential early biomarkers of cancer. The evidence, though largely built on case reports and small cohorts, is consistent enough to justify a low threshold for oncologic referral when ocular findings refuse to obey the rules of common disease.

Keywords: occult malignancy; paraneoplastic retinopathy; cancer-associated retinopathy; ocular metastasis; masquerade syndrome; early cancer detection; biomarker; fundus biomicroscopy

1. Introduction

Every clinician who has practised long enough carries a memory of a case in which the eye gave the first warning. A retired teacher complains that streetlights have begun to smear and flicker; her fundus looks nearly normal, her acuity is 20/20, yet within six months she is found to harbour a small-cell carcinoma of the lung. A middle-aged man is sent to the eye clinic with "recurrent conjunctivitis" that will not settle; biopsies of his eroded lids eventually point to an occult lymphoma. These are not curiosities for the case-book. They illustrate a measurable, biologically coherent phenomenon: tumours shed antigens, cytokines, and embolic cells, and the eye—with its immense neural bandwidth, its fenestrated choroidal circulation, and its immune-privileged interior—registers these signals with uncomfortable fidelity.

The concept is older than molecular oncology. The term "masquerade syndrome" entered the ophthalmic lexicon in 1967, describing a conjunctival carcinoma misdiagnosed as stubborn inflammation, and it has since expanded to cover every ocular condition that wears the costume of a banal disease. Paraneoplastic syndromes as a whole are estimated to complicate 7–15% of cancers, and while ocular forms are rare, they are disproportionately important because they so often arrive before the tumour itself. A 2025 systematic review of 147 patients across six paraneoplastic ocular syndromes found that the underlying neoplasm was identified only after the visual complaint in the overwhelming majority of cases—in 81% of cancer-associated retinopathy (CAR) and 100% of paraneoplastic uveitis.

This article asks a deliberately provocative question: can we treat certain visual changes as early biomarkers of cancer? A biomarker, strictly defined, is a characteristic that is objectively measured and evaluated as an indicator of normal or pathogenic processes. Visual symptoms fail that test in their raw form—subjective, noisy, non-specific. But when a stereotyped ocular signature is combined with confirmatory electrophysiology, circulating autoantibodies, and high-resolution imaging, the composite begins to behave like a genuine early-warning system. We review the evidence mechanism by mechanism, separating what is established from what is

merely plausible, and close with a practical framework for the clinician who meets these patients first.

2. Why the Eye Sees Cancer First

Three anatomical facts explain the eye's sentinel role. First, the retina and optic nerve are embryologically brain; they translate subtle biochemical injury into symptoms—photopsia, nyctalopia, dyschromatopsia, field loss—at thresholds far below those that produce measurable neurological deficit elsewhere. A patient notices a scotoma caused by a few thousand dysfunctional photoreceptors long before a comparably sized lesion in the cerebral cortex would declare itself. Second, the choroid is the most highly perfused tissue per gram in the body, and its vessels, unlike retinal capillaries, are fenestrated. Circulating tumour emboli, immune complexes, and onconeural antibodies therefore reach the uveoretinal compartment with unusual efficiency; this is why choroidal metastasis, though a small fraction of cancer spread, is so visually eloquent. Third, the eye is directly observable. No other microvascular bed can be photographed, angiographed, and optically cross-sectioned in the clinic chair within minutes, making the eye an accidental window on systemic disease.

Mechanistically, the ocular clues to occult malignancy fall into three families: (i) immune-mediated paraneoplastic injury, in which tumour antigens provoke cross-reactive autoantibodies against retinal or optic nerve components; (ii) haematogenous spread, in which viable tumour cells seed the uveal tract, orbit, or retina; and (iii) neuro-ophthalmic syndromes, in which remote tumour effects disturb ocular motility, pupillary function, or intracranial visual pathways. Table 1 summarises the principal paraneoplastic ocular syndromes.

Syndrome	Typical visual phenotype	Associated antibodies	Common underlying malignancies
Cancer-associated retinopathy (CAR)	Rapid, bilateral, painless loss of acuity; photopsias; ring scotomas; nyctalopia; photoaversion	Anti-recoverin, anti- α -enolase, others	Small-cell lung carcinoma, gynaecological cancers
Melanoma-associated	Night blindness, photopsias, shimmering	Anti-bipolar cell (TRPM1-related)	Cutaneous and uveal melanoma (often at recurrence)

retinopathy (MAR)	photopsias; relatively preserved central acuity early		
Bilateral diffuse uveal melanocytic proliferation (BDUMP)	Bilateral red fundus patches, rapidly multiplying pigmented uveal tumours, exudative detachment, fast cataract	Often seronegative; occasional anti-transducin	Lung (men), gynaecological (women); many others
Acute exudative polymorphous vitelliform maculopathy (AEPPVM / PVM)	Multifocal yellow vitelliform macular lesions with serous detachment	Variable	Melanoma, leukaemia/lymphoma, lung, renal, pancreatic
Paraneoplastic optic neuropathy (PON)	Subacute bilateral visual loss with disc oedema and vitritis	Anti-CRMP5 (anti-CV2), amphiphysin	Small-cell lung carcinoma, lymphoma, thymoma
Paraneoplastic uveitis (PU)	Chronic anterior/posterior uveitis resisting steroids	Occasionally CRMP5	Pulmonary cancers, lymphoma

Table 1. The principal paraneoplastic ocular syndromes and their typical oncologic associations.

3. The Paraneoplastic Retinopathies: Immunity with a Grudge

Cancer-associated retinopathy is the archetype and the cautionary tale. First described in association with small-cell lung cancer, CAR typically announces itself with abrupt, bilateral, relentlessly progressive visual decline over weeks—photopsias like a swarm of sparks, glare intolerance, washed-out colour vision, and night blindness reflecting

combined rod and cone failure. The cruel diagnostic trap is that the fundus can look nearly pristine early on; disease activity is measured in retinal function, not retinal appearance. Electroretinography shows extinguished or severely attenuated scotopic and photopic responses, and serum testing frequently reveals antiretinal antibodies, classically anti-recoverin, a calcium-binding photoreceptor protein whose aberrant expression by tumour cells breaks immune tolerance. The tumour, in effect, vaccinates the patient against his or her own retina.

The prognosis data sharpen the argument for early detection. In the systematic review cited above, CAR carried the worst visual outlook of all six syndromes, with nearly half of patients deteriorating despite treatment—yet an oncologic diagnosis within six months of symptom onset was significantly associated with better visual outcome ($p = 0.03$). In other words, the eye's warning is only useful if someone acts on it. Melanoma-associated retinopathy follows a related but distinct script: shimmering photopsias and night blindness in a patient with known—or about-to-be-discovered—melanoma, mediated by antibodies directed at ON-bipolar cell antigen TRPM1. BDUMP is rarer but more dramatic, seeding the uveal tract with dozens of pigmented tumours and cataracts that mature within months; in roughly half of reported cases the eye disease precedes the cancer diagnosis, and median survival thereafter is measured in months, underlining how aggressively the underlying malignancy should be hunted.



Figure 1. Leukocoria in a child—the classic white pupillary reflex of retinoblastoma, the most striking example of an ocular sign preceding systemic consequences of malignancy. (Image: The Eye Cancer Network.)

In children, the logic inverts delightfully: the ocular sign is the disease. Leukocoria—a white pupillary reflex noticed by a parent in a photograph—remains the commonest presenting feature of retinoblastoma, and its recognition, however accidental, directly

drives survival. The principle generalises: an eye that looks wrong should never be dismissed, at any age.

4. Metastatic Disease to the Eye: The Tumour That Chose the Window

The uveal tract is the preferred soil for circulating cancer cells within the globe, and breast and lung carcinomas dominate the epidemiology simply because they dominate cancer incidence overall. Choroidal metastases classically appear as creamy-yellow, placoid or dome-shaped subretinal lesions in the posterior pole, often accompanied by exudative detachment; patients report a shadow drifting through the field, distortion, or painless blur. Breast cancer tends to produce solitary, late lesions in patients with known disease, whereas lung cancer is notorious for presenting simultaneously with—or even before—the primary diagnosis, because a small pulmonary primary can shed emboli while still radiologically occult. Up to a tenth of patients with choroidal metastases are asymptomatic, the lesion found only because someone looked.

Retinal metastasis is far rarer and therefore more treacherous. A 2024 systematic review of published cases found the dominant primary sites to be lung, gastrointestinal tract, and breast, with three recurring clinical patterns: patchy retinal infiltrates masquerading as infective retinitis, an elevated retinal mass, and punctate infiltrates scattered like seeds. Because these mimic toxoplasmosis or viral necrotising retinitis, the correct answer is frequently reached only after the "infection" defies antimicrobials. Final visual acuity was 20/200 or worse in two-thirds of affected eyes—a reminder that retinal metastasis is not only a diagnostic crisis but an oculo-vascular emergency.

The ophthalmic literature preserves vivid cases in which the eye was the first and only evidence of systemic cancer: a painful blind eye biopsied for suspected uveitis that proved to be metastatic lung carcinoma; vitelliform maculopathy preceding leukaemic relapse; BDUMP in a well patient whose sole abnormality, after exhaustive work-up, was a tiny ovarian primary found on positron-emission tomography. Individually these are anecdotes; collectively, across dozens of independent reports, they constitute a signal.



Figure 2. Fundus photograph and B-scan ultrasonography of a choroidal metastasis: a yellow, elevated subretinal mass with associated detachment. Breast and lung primaries predominate. (Reproduced from a review of metastatic tumours to the eye, Eye.)

Ocular clue	How it presents	Occult malignancies to exclude first
Rapid bilateral photoreceptor dysfunction (photopsia, nyctalopia, ring scotoma) with quiet fundus	Weeks of painless progressive loss; ERG extinguished or attenuated	Small-cell lung cancer; gynaecological primaries (CAR); melanoma (MAR)
Multiple new pigmented uveal tumours + exudative detachment + fast cataract (BDUMP)	Bilateral, symmetrical; angiographic red patches precede tumours	Lung, ovarian/uterine/renal, pancreatic, lymphoma
Creamy subretinal posterior-pole mass with detachment	Visual shadow, metamorphopsia, floaters; may be asymptomatic	Lung (including occult primary), breast, GI, renal, melanoma

Vitreous cells / "uveitis" unresponsive to steroids	Chronic smouldering inflammation, no infection found	Intraocular (vitrectomy biopsy): lymphoma; systemic: lung, leukaemia/lymphoma
New bilateral optic disc oedema with vitritis	Subacute acuity and field loss, often painful	Small-cell lung cancer, lymphoma, thymoma (anti-CRMP5)
Adult-onset Horner syndrome, diplopia, or proptosis	Painless ptosis/miosis; gaze palsy; globe displacement	Apical lung (Pancoast), metastatic orbital disease, nasopharyngeal
Leukocoria (child) or unilateral "refractory conjunctivitis"	White reflex on photos; erosive cicatrising conjunctivitis	Retinoblastoma; paraneoplastic pemphigus / ocular surface neoplasia

Table 2. Red-flag ocular presentations and the occult malignancies they most often conceal.

5. Masquerades and Neuro-Ophthalmic Whispers

The masquerade family deserves special respect because its members are defined by failed recognition. Primary intraocular lymphoma—usually a diffuse large B-cell lymphoma allied to primary CNS lymphoma—specialises in impersonating chronic vitritis in older adults, complete with steroid responsiveness that persuades everyone to stop looking. Diagnosis typically requires diagnostic vitrectomy with cytology and flow cytometry, and the CNS should be imaged in every case. Paraneoplastic pemphigus conjures cicatrising conjunctivitis with corneal melting; Sweet syndrome dresses as episcleritis or panuveitis; acanthosis nigricans quietly thickens the lid margins. Each is rare, but each is a named chapter in the same book: inflammation that behaves oddly should be biopsied, not merely suppressed.

Neuro-ophthalmology contributes quieter clues that are easy to rationalise away. New-onset Horner syndrome in an adult smoker—painless ptosis and miosis—can be the only footprint of an apical lung tumour. Opsoclonus ("dancing eyes") in a toddler should trigger a search for neuroblastoma; roughly half of children with opsoclonus harbour one. Lambert–Eaton myasthenic syndrome announces itself with fatigable ptosis and diplopia years before a small-cell cancer surfaces in a minority of patients. Paraneoplastic optic neuropathy, most often carrying anti-CRMP5 antibodies, blends

disc swelling, vitritis, and relentless bilateral field loss, and lung cancer again tops the list of accomplices. The common denominator is unexplained, bilateral, progressive dysfunction in a patient who otherwise feels well.

6. From Red Flag to Diagnosis: A Practical Pathway

A workable approach begins with the humility to accept that the eye may be reporting on a problem elsewhere. Stereotyped presentations—Table 2 provides a checklist—should trigger a defined sequence: document the phenotype thoroughly (visual fields, colour vision, fundus photography, autofluorescence, OCT, fluorescein angiography); test function objectively (pattern and full-field ERG); search for onconeural and antiretinal antibodies in serum, remembering that antibody panels aid but do not prove the diagnosis, since antiretinal antibodies occur without cancer and some paraneoplastic syndromes are seronegative; and then hunt the tumour with age-appropriate imaging, typically contrast CT of the chest, abdomen, and pelvis, with whole-body FDG-PET where conventional imaging is unrevealing and suspicion remains high. Multidisciplinary hand-off—ophthalmology to neurology to oncology—is not a courtesy but the core of the diagnosis. When biopsy of a suspicious ocular lesion is feasible and safe, it should be pursued, because ocular tissue can be the most accessible specimen of a still-hidden systemic cancer, and modern immunohistochemistry (including lineage markers such as GATA-3, TTF-1, and SOX10) can identify the primary from a few cells.

Treatment logic follows from mechanism. Where the tumour can be found and treated—surgery, chemotherapy, targeted therapy, or immune checkpoint blockade—paraneoplastic visual disease may stabilise, and BDUMP in particular sometimes regresses dramatically after removal of the primary. Local ocular therapy (corticosteroids, plasmapheresis, intravitreal anti-VEGF, ocular radiotherapy for metastases) is temporising at best, and CAR remains stubbornly resistant; the honest counselling point for patients is that the visual prognosis is guarded even when the cancer is found early, though early oncologic treatment offers the best—and sometimes only—chance of arrest.

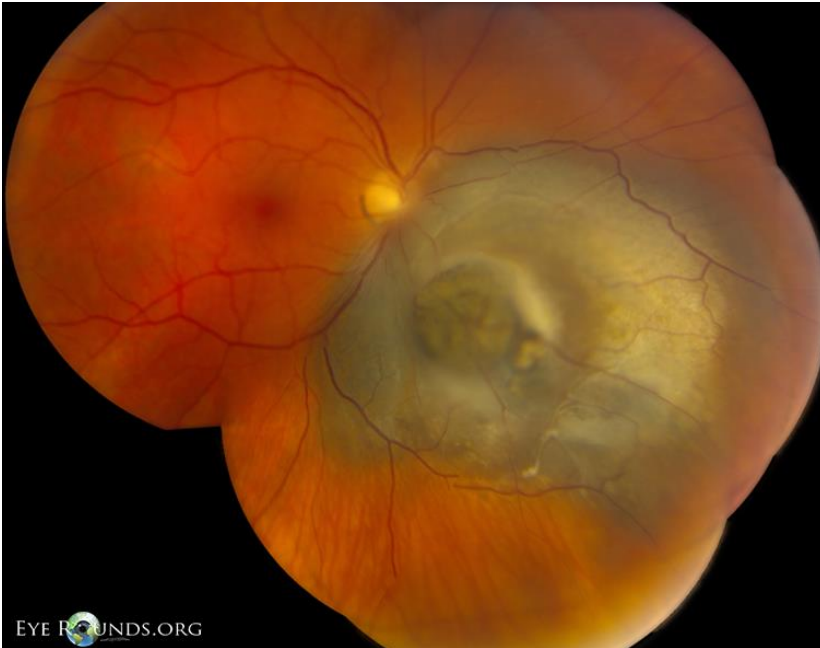


Figure 3. Choroidal melanoma in a 58-year-old woman: a pigmented posterior-pole mass with exudative retinal detachment—an example of primary intraocular malignancy detected through routine fundus examination. (EyeRounds, University of Iowa.)

7. Can Visual Changes Truly Function as Early Biomarkers?

Scepticism is warranted, and the honest answer is: partially, and conditionally. Against the biomarker concept stand real weaknesses. The syndromes are rare; CAR, MAR, BDUMP, and their siblings together account for a few hundred published cases. Sensitivity is unknowable—there is no screening programme that counts the cancers missed because no eye complained. Specificity is imperfect: antiretinal antibodies appear in autoimmune retinopathy without cancer, and uveal metastases can be mimicked by choroidal naevi, haemangiomas, and inflammatory lesions. And publication itself is biased toward the dramatic case in which the eye truly came first.

Set against that are three strengths that rare diseases rarely enjoy. The phenotype-to-cancer link is mechanistically intelligible—named antibodies against named retinal antigens produced by named tumours. The temporal pattern is consistent across independent reports and continents: in most series the visual complaint precedes tumour detection, by weeks in CAR and lymphoma, sometimes by years in breast and prostate disease. And the test is cheap, non-invasive, and repeatable. The pragmatic synthesis is that these ocular syndromes should be regarded as "sentinel phenotypes" rather than laboratory biomarkers: they are not screening tools for the general

population, but in the individual patient with a compatible picture, they function exactly as an early-warning biomarker is supposed to—altering pre-test probability enough to justify an aggressive search for a cancer that would otherwise declare itself later, larger, and less curably.

8. Conclusion

The eye's relationship with occult malignancy is not folklore; it is anatomy plus immunology, repeatedly confirmed at the bedside and under the microscope. Paraneoplastic retinopathies, metastatic seeding, neuro-ophthalmic syndromes, and masquerade inflammations each provide a route by which a hidden tumour becomes visible—or symptomatic—before it becomes palpable, imagable on routine studies, or clinically declared. The clinician's task is to honour these warnings with the same seriousness accorded to a suspicious mole or an unexplained weight loss: document, test, refer, and search. As ophthalmic imaging, autoantibody profiling, and molecular diagnostics converge, the day may come when a defined ocular signature plus a blood test reliably localises an occult primary. Until then, the dilated fundus examination remains arguably the most underused early-cancer diagnostic in medicine—a window through which the body sometimes confesses its secrets first.

References

1. Beuzit S, et al. Paraneoplastic ocular syndromes: a systematic review of epidemiology, diagnosis and outcomes (2010–2023). *Int Ophthalmol*. 2025;45:s12348-025-00534-1.
2. Rahimy E, Sarraf D. Paraneoplastic and related retinopathies: an update on pathogenesis, diagnosis and management. *Ann Eye Sci*. 2024;9:7643.
3. Rishi P, Rishi A, Gupta H, Swaminathan M, Chhablani J. Insights into retinal metastasis from systemic carcinoma. *J Clin Med*. 2024;13(20):6037.
4. Garrido-Hermosilla AM, et al. GATA-3 biomarker as a confounding factor in a patient with intraocular metastasis from squamous cell carcinoma of the lung. *Arch Soc Esp Oftalmol*. 2025.
5. Li D, et al. Retinal metastasis from lung adenocarcinoma: a case report. *Front Oncol*. 2025;15:1616331.
6. Singh AD. Metastatic tumours to the eye: review of metastasis to the iris, ciliary body, choroid, retina, optic disc, vitreous, and/or lens capsule. *Eye*. 2022 (Nature).

7. American Academy of Ophthalmology. How to spot ocular metastases. EyeNet Magazine, AAO; 2004.
8. Cleveland Clinic Consult QD. Cancer metastasis to the eye takes many forms. 2023.
9. EyeWiki. Ophthalmologic manifestations of paraneoplastic syndromes; and Retinal metastasis. American Academy of Ophthalmology (accessed 2026).
10. Stanford Neuro-Ophthalmology. Paraneoplastic syndromes in neuro-ophthalmology. 2017.
11. Jakobiec FA, et al. Photodynamic therapy for solitary retinal metastasis from breast carcinoma. Eye. 2007 (Nature).
12. The Retina Institute. Cancer-associated retinopathy and paraneoplastic retinopathies (clinical review).
13. EyeRounds, University of Iowa. Choroidal malignant melanoma: 58-year-old female with pigmented retinal lesion and exudative retinal detachment.
14. The Eye Cancer Network. Retinoblastoma and leukocoria image gallery.
15. Owczarek W, et al. Ocular manifestations of dermal paraneoplastic syndromes. Postepy Dermatol Alergol. 2018.