Case report

UVEITIS IN PARANEOPLASTIC SYNDROME: ABOUT 4 CASES

**Abstract:**

Paraneoplastic ocular disorders are rare conditions that may precede or accompany a cancer

diagnosis. These disorders result from an autoimmune response that targets tumor-associated

antigens aberrantly expressed in ocular tissues, affecting the retina, optic nerve, and

vasculature. Common types of paraneoplastic ocular disorders include cancer-associated retinopathy, paraneoplastic optic neuropathy, chronic uveitis, and melanoma-associated retinopathy.

Diagnosis is particularly challenging in elderly patients with ophthalmic comorbidities, as the

eye is not directly affected by the tumor. The diagnosis relies on ophthalmologic

examinations, ocular ultrasound, and autoantibody testing to facilitate oncological evaluation.

Management primarily focuses on treating the tumor, often in conjunction with immunomodulatory therapies. While corticosteroids may help reduce inflammation, their efficacy can vary. A multidisciplinary approach that includes ophthalmologists, oncologists, geriatricians, and internists is essential for optimizing patient outcomes.

This article presents four cases of paraneoplastic uveitis associated with bladder cancer, thyroid cancer, multiple myeloma, and monoclonal gammopathy, emphasizing the diagnostic complexity of this condition.

## Key words: uveitis, paraneoplastic, case report, cancer , Diagnosis

# INTRODUCTION

Paraneoplastic syndromes refer to clinical conditions caused by a distant tumor process, unrelated to direct tumor invasion or compression. These syndromes often stem from an autoimmune response against tumor antigens that are mistakenly expressed in healthy tissues (1). While they can affect multiple organ systems, ocular involvement is uncommon but clinically significant, as it may serve as an early indicator of an underlying malignancy.

Paraneoplastic ocular disorders result from an immune cross-reaction, where antibodies targeting tumor antigens also attack ocular structures, leading to inflammation or degeneration (1). These conditions can affect various parts of the eye, including the retina, optic nerve, and vasculature, giving rise to diverse clinical presentations such as cancer- associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic optic neuropathy (2), and chronic uveitis that does not respond to standard treatment.

Diagnosing these conditions in elderly patients is particularly challenging due to the frequent presence of age-related eye diseases such as cataracts and age-related macular degeneration (AMD). Furthermore, because the tumor does not directly involve the eye, these syndromes can be difficult to recognize, often leading to delays in diagnosis and cancer treatment. A deeper understanding of these conditions may improve early detection and prompt investigation into an underlying malignancy.

Diagnosis relies on a thorough ophthalmologic examination, testing for specific autoantibodies, and targeted oncological evaluation. Treatment primarily focuses on managing the underlying cancer, often in combination with immunomodulatory therapies to limit immune-related damage to ocular tissues.

This report presents four cases of ocular paraneoplastic syndromes associated with systemic cancers. Through these cases, we emphasize the mechanisms underlying these conditions, key diagnostic and therapeutic strategies, and the importance of close collaboration between ophthalmologists, internists, geriatricians, and oncologists to optimize patient care.

# Case presentation

**CASE 1: UROTHELIAL CARCINOMA OF THE BLADDER**

The patient was a 73 years old man, a chronic smoker (20 pack-years for 60 years) and occasional cannabis and alcohol user, who had consulted us about a progressive decline in visual acuity in his right eye over the past month, accompanied by pain, redness and swelling of the right eye, all evolving in a context of decline general condition, with anorexia, weight loss (not quantified) and sweating nocturnal.

Ophthalmological examination revealed visual acuity assessed at 3/10 bilaterally, conjunctival hyperemia in the right eye, clear cornea bilaterally, four-cross Tyndall in the right eye and one- cross Tyndall in the left eye, iridocrystalline synechiae at 3 and 9 o'clock in the right eye, Ocular tone was normal at 12mmHg bilaterally, the fundus showed a vitreous Tyndall bilaterally, the

retina was flat in the left eye, and in the right eye passage was impeded, while an ocular ultrasound scan showed a posterior choroidal detachment in the right eye.

Clinical examination revealed a sensitive mass in the hypogastric region, associated with irritative disorders of the lower urinary tract of the pollakiuria and micturition urgency type, evolving for three years and associated with terminal clotting hematuria. A bladder ultrasound revealed an intravesical budding lesion process (21x7mm) with no upstream impact, complemented by a CT urogram showing a tumor-like lesion process in the bladder. The patient was then scheduled for a transurethral resection of bladder tumor (TURBT), the report of which was as follows pathology indicated urothelial carcinoma.

Following endoscopic resection of the tumor, the patient received intravesical BCG chemotherapy. Local corticosteroid therapy was initiated for the ocular involvement, with notable clinical improvement. Regular follow-up was set up to prevent tumor recurrence and monitor ophthalmological evolution.

# CASE N°2: MULTIPLE MYELOMA

The patient was a 77-year-old woman with a 22-year history of arterial hypertension controlled by amlodipine (10 mg/d), who had undergone cataract surgery in her right eye 2 years previously and had a history of passive smoking. Her symptoms had been presenting for three years, with a bilateral decrease in visual acuity and recurrent episodes of ocular redness. This symptomatology was accompanied by inflammatory arthralgias involving both elbows, both wrists, the cervical, dorsal and lumbar spine, all evolving in a context of subjective dry mouth syndrome, paresthesia of the upper limbs, feverish sensation and altered general condition consisting of asthenia and weight loss of 17kg in one year.

Ophthalmological examination revealed visual acuity assessed at 3/10 in the right eye and positive light perception in the left eye; the cornea was clear bilaterally; examination of the anterior segment of both eyes revealed sequelae of a former bilateral granulomatous anterior uveitis with koeppe and busacca nodules, hyalitis in the posterior segment the right eye and a total cataract with iridocrystalline synechiae in the left eye, intraocular tone was 12 mmHg bilaterally, and the Schirmer test was negative. On fundus, the passage of light was obstructed, and ocular ultrasound showed hyperechoic vitreous in both eyes, with retina flat.

The patient's clinical examination revealed spinal pain on pressure of the cervical and dorsolumbar spinous processes, pain on active and passive mobilization of the elbow and wrist joints, and a thyroid gland.

Complementary examinations included objective cervical ultrasound of thyroid nodules classified as EU-TIRADS 3 with correct TSH. Infectious disease workup: viral serologies (HIV, Syphilis, EBV, CMV, HBV, HCV) and Quantiferon were all negative. Anti-SSA and SSB antibodies were negative. Plasma protein electrophoresis showed hypoalbuminemia at 29g/l, peak beta-2- globulin at 12.6 g/L and hypogammaglobulinemia at 5.89g/l, serum immunofixation revealed the presence of monoclonal kappa light-chain immunoglobulin A, with kappa/lambda ratio of 1.53; beta-2-microglobulin was elevated to 4.65 mg/L (without renal impairment). The blood count

showed an anemia of 10.5 normochromic normocytic aegerative with a reticulocyte count of 65,000, TSH correct, Vit B 9 and B 12 normal. Myelogram showed 8% plasmacytosis, suggestive

of multilineage myelodysplastic syndrome without excess blasts. The diagnosis of monoclonal gammopathy of undetermined significance was then made in view of the kappa light-chain monoclonal gammopathy, the beta2 globulin monoclonal peak at 12.6g/l, negative Bence Jones proteins, and plasma cells at 8% on the myelogram, for the CRAB criteria, calcemia was correct at 85mg/l, glomerular filtration rate at 86 ml/min, no lytic lesions on low-dose CT scan, and anemia at 10 aregenerative in the context of amyelodysplastic syndrome.

The patient was put on systemic corticosteroid therapy, with significant improvement in ocular symptoms. Regular monitoring by plasma protein electrophoresis had enabled early detection of transformation to multiple myeloma, and so the patient was treated with a VCD protocol (bortezomib, cyclophosphamide and dexamethasone).

# CASE 3: MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

A 72-year-old man with a history of active smoking weaned 11 years ago, presented with acute unilateral visual acuity loss in the right eye for the past 2 months, associated with inflammatory arthralgias of the large and medium joints and bilateral inflammatory talalgias, with no skin, digestive, respiratory or neurological signs, all evolving in a context of apyrexia, and a slight decline general condition.

Ophthalmological examination revealed visual acuity of 4/10 in the right eye and 7/10 in the left, mild corneal edema in the right, a four-cross Tyndall in the right and a one-cross Tyndall in the left with bilateral iridocrystalline synechiae and fine retrodescemetic precipitates in the right with a dense three-cross hyalite and vitreous Tyndall. Fundus passage was obstructed, and an ocular ultrasound showed a right posterior choroidal detachment.

The patient's clinical examination revealed pain in the palpation of the sternocostal joints and pain when the sacroiliac joints were drawn together.

Further investigations revealed positive CMV serology, with IgG at 235 IU/mL and negative IgM. The patient was started on valaciclovir 3g/d, with subjective and objective improvement in face of regression of Tyndall's ophthalmological examination, but without clear negativation, with a slightly active aspect anterior and intermediate uveitis. To complete the work-up and explain the persistence of uveitis despite subjective improvement, Quantiferon was negative, HLA B 27 negative, plasma protein electrophoresis showed a monoclonal peak of beta-2-globulin at 11 g/L, serum immunofixation revealed the presencemonoclonalimmunoglobulin G at 1.8 g/dL,

24-hour proteinuria was negative, myelogram showed plasma cells at 5%, all of which pointed to MGUS.

Treatment included antiviral therapy (valaciclovir) and systemic corticosteroids, with marked improvement and normalization of the ophthalmological examination. Hematological follow- up was instituted to detect progression to multiple myeloma.

# CASE 4: THYROID CARCINOMA

The patient was a 71-year-old man with a history of type II diabetes on oral antidiabetics. the patient presented with a progressive bilateral decrease in visual acuity associated with a chronic dry cough that had been evolving for three years, in a context of weight loss of 15kg in 6 months, with no other signs, notably no fever, no night sweats, no joint involvement, no dry syndrome, no ENT, no digestive or neurological involvement.

Ophthalmological examination revealed bilateral granulomatous panuveitis. The acuity visual acuity in the right eye was 4/10, in left 5/10, bilateral two-cross Tyndall, bilateral Koeppe's and Busacca's nodules, ocular tone 18mmHg, diffuse choroidal nodules on fundus.

The patient's clinical examination revealed a slightly enlarged thyroid, while the rest of the somatic examination was unremarkable.

On further examination, the infectious workup (viral and tuberculosis serologies) for the ocular involvement was negative. The inflammatory workup was also negative, with negative CRP, and the immunological workup was negative for sarcoidosis, vasculitis or granulomatosis with polyangiitis. A thyroid ultrasound revealed a thyroid nodule classified EU-TIRADS 5 measuring 22x17mm, and a cytopunction revealed thyroid carcinoma.

Total thyroidectomy was performed, followed by radiotherapy with iodine 131. Systemic corticosteroid therapywasinitiated to manageocularmanifestations, withafavorable outcome.

# DISCUSSION

Paraneoplastic uveitis is a rare entity but poses a diagnostic and therapeutic challenge due to its association with an often-unknown underlying tumor process. They happen in the context of an autoimmune response targeted against cancer antigens shared between the cancer and ocular tissues. This aberrant recognition by the immune system may take various clinical forms from anterior uveitis to granulomatous panuveitis as demonstrated in the reported cases.

Ocular paraneoplastic syndrome may present as carcinoma-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), bilateral diffuse uveal melanocytic proliferation, optic neuropathy, paraneoplastic vitelliform retinopathy, opsoclonus-myoclonus syndrome, or Lambert-Eaton myasthenic syndrome (3).

A visual acuity loss may be caused by uveitis, retinitis, optic neuropathy, or other neurological changes. CAR and MAR are among the most frequently seen clinical types of paraneoplastic syndrome. However, intraocular inflammation may be present as panuveitis or optic neuropathy (3).

There have been reported in literature some cases of presumed paraneoplastic uveitis. It can involve any part of the uveal tract; the manifestations are protean (4). The most classic form is that of intermediate uveitis secondary to Ac anti-CV2 (or anti-CRMP5) (5). The clinical picture of bilateral cortico-dependent vitritis with bilateral retinal vasculitis, secondary associated with cerebellar ataxia, that Antoine et al. identified antibodies to anti-CV2 antibodies in 1993 (6).

There have been also reported some cases of an unusual unilateral or bilateral macular detachment that were further associated to benign (polyclonal gammopathy) or malignant (multiple myeloma and Waldenström’s macroglobulinemia) systemic plasma cell dyscrasias (8). It has been also reported in 1986, the first case of Macular oedema associated to multiple myeloma (9).

In another case report, an adult captive male owl who was presenting an unilateral blepharospasm revealing a bilateral anterior uveitis and a corneal ulceration in the left eye. It was treated with oral and topical nonsteroidal anti-inflammatory medications and a topical antibiotic. On physical examination, the owl was quiet and had difficulty standing and ambulating. Five firm multilobular and immobile masses were identified overlying the pectoral muscle and sternum. Biopsy revealed a sarcoma. The mass was diagnosed as a pleomorphic spindle cell sarcoma with features of rhabdomyosarcoma, liposarcoma, and osteosarcoma. This report described an apparent ocular manifestation of systemic disease in an avian species with clinically diagnosed anterior uveitis (10).

## Pathophysiological mechanisms

Many of the paraneoplastic 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 tumor antigens and normal host tissue (2)

The [pathophysiology](https://www.sciencedirect.com/topics/medicine-and-dentistry/pathophysiology) of these syndromes is not fully understood, but autoimmunity plays an important role. Some neoplastic cells can develop antigens with epitopes (protein peptide sequences) like those present in healthy organs (molecular mimicry). The immune system develops a humoral and cellular response against the tumor which, by cross-reaction, will also affect healthy tissues and organs in which these antigens are present (7).

In these cases, the autoantibodies target tumor antigens cross-react with ocular expressed proteins, inducing an inflammatory cascade. This response is compounded by the activation of the immune cells in the tumor milieu causing systemic inflammation that breaches the blood- ocular barrier.

In CAR and MAR, anti-retinal autoantibodies like anti-recoverin as well as anti-ENOA have been reported. Yet, in uveitis associated with paraneoplastic syndromes, mechanisms are not well defined, and seem to involve immune reactions directed against uveal pigment cells.

## Differential diagnosis and diagnostic approaches

The diagnosis of paraneoplastic uveitis relies on several clinical and paraclinical arguments.

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| Before searching for paraneoplastic causes, it is crucial to search for all the possible both |
| infectious and non-infectious diseases that may cause granulomatous inflammation of the uveal |
| tract (uveitis). Starting with the infectious causes, it can be Tuberculosis, Syphilis, Herpes viruses, |
| Cytomegalovirus, Trematodes, Toxoplasmosis, Post-streptococcal infections. And NON- |

INFECTIOUS: Sarcoidosis, Multiple sclerosis, Lymphoma, Lens-induced (11).

Diagnosis is made in cases of atypical uveitis, unresponsive to standard treatments, with systemic symptoms of unexplained etiology (general conditions deterioration, changed nutritional status, target as arthralgias, inflammatory syndromes). The work-up should include:

* Comprehensive ophthalmological workup, fluorescein angiography and optical coherence

tomography (OCT) for retinal and uveal injury evaluation.

* A search for certain autoantibodies, for example: anti-recoverin, anti-CRMP-5, anti- amphiphysin.
* Directed imaging according to manifestations (thoraco-abdomino-pelvic CT, brain MRI) in search for an underlying cancer.
* Cerebrospinal fluid analysis, in case of suspected paraneoplastic optic neuropathy.

The role of hematological investigation is underscored by our cases, where plasma protein electrophoresis and myelograms were used to discover monoclonal gammopathies associated with ocular pathology.

## Management and prognosis

The therapeutic approach is dependent on management of primary malignancy. To modulate the self-limiting inflammatory response, local or systemic corticosteroid therapy is frequently initiated to mitigate the ocular symptomatology. For lasting response, the primary tumor is usually required to be treated as well.

In reported cases:

* Ocular involvement had improved following RTUTV and intravesical BCG instillations in the patient with urothelial carcinoma.
* The multiple myeloma patient had a VCD protocol requirement, with ophthalmological manifestations stabilized.
* The MGUS patient had been doing well on corticosteroids and valaciclovir, with careful hematological follow-up.
* The thyroid carcinoma was treated with total thyroidectomy and radiotherapy and ophthalmological signs regressed.

The prognosis of paraneoplastic uveitis is variable and depends on both the evolution of the tumor pathology and the earliness of the diagnosis. Patients should be followed for prolonged periods, as they are susceptible to tumor recurrence or evolution to myeloproliferative syndrome.

# CONCLUSION

Uveitis associated with paraneoplastic syndromes remains a complex but clinically significant diagnostic entity. Multidisciplinary collaboration between ophthalmologists, internists, geriatricians and oncologists is essential to optimize the management of these patients and improve their visual and vital prognosis.

**Limitations:** limitations of this report are lack of clinical images describing uveitis and lack of funds to search for specific antibodies such as anti-recoverin, anti-CRMP-5, and anti- amphiphysin. The fact that these cases of uveitis revealed underlying malignant cause may deserve to be known for early detection and treatment.

**Ethical Approval:**

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

**Consent**

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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