Case report

UVEITIS IN PARANEOPLASTIC SYNDROME : ABOUT 4 CASES

Abstract :

Ocular disorders in paraneoplastic syndromes are the least common manifestations of the disease that may precede or accompany the diagnosis a underlying cancer disease. These ocular pathologies are mainly result of an autoimmune response directed against tumor antigens that are aberrantly expressed in ocular tissues. This cross-immune reaction leads to inflammation or degradation of ocular tissues, affecting structures such as the retina, optic nerve and ocular vasculature. The most common clinical forms include cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy, chronic uveitis and melanoma-related retinopathy.

Ocular paraneoplastic manifestations, extremely varied, can be particularly complex to diagnose, especially in elderly patients, in whom age-related ophthalmological comorbidities such as cataract or age-related macular degeneration (AMD) are often present. In addition, the absence of direct tumour signs in the eye complicates recognition of these paraneoplastic syndromes, often prolonging the diagnostic delay and thus delaying appropriate oncological management.

Diagnosis is based on a combination detailed ophthalmological examinations, including ocular ultrasound evaluation and biological tests specific autoantibodies. This is essential to identify patients requiring oncological exploration, enabling early detection of underlying cancer. Therapeutic management focuses on treatment of the primary tumor, often combined with immunomodulatory therapies to control the autoimmune response. Immunosuppressive treatments, such as corticosteroids, are used reduce ocular inflammation, although their efficacy varies according to the intensity and chronicity of symptoms.

Multidisciplinary management involving ophthalmologists, oncologists, geriatricians and internists is crucial to optimizing patients' clinical outcomes. Regular follow-up is also essential to adjust treatment according to evolution of tumor and ocular damage, thus reducing the risk of long-term complications and improving patients' quality of life.

This article presents four cases of paraneoplastic uveitis, revealing bladder cancer, thyroid cancer, multiple myeloma and monoclonal gammopathy of undetermined significance, illustrate the diversity of clinical manifestations and the associated diagnostic complexity.

INTRODUCTION

Paraneoplastic syndromes are a group of clinical manifestations secondary to a distant tumor process, with no direct relation to neoplastic infiltration or tumor compression.

These syndromes generally result an autoimmune response directed against tumor antigens aberrantly expressed in certain tissues. Among the various systemic manifestations of paraneoplastic syndromes, ophthalmological involvement remains relatively rare, but is of major clinical importance because of its potential to reveal an underlying cancer.

Paraneoplastic ocular manifestations are often the result an immune cross-reaction, where autoantibodies directed against tumor antigens interact with ocular structures, leading to inflammatory or degenerative alterations. These alterations can affect various structures in eye, including the retina, optic nerve and ocular vasculature, leading to a variety of clinical pictures such as cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic optic neuropathy or chronic uveitis resistant to conventional treatments.

In elderly patients, these manifestations are particularly difficult to diagnose due to the high prevalence of age-related ophthalmological comorbidities, such as cataracts or age-related macular degeneration (AMD). What's more, the absence direct tumor involvement makes recognition of these syndromes even more difficult. As a result, diagnostic delays can be prolonged, delaying appropriate oncological treatment. A better understanding of these conditions would enable earlier recognition of ocular manifestations of paraneoplastic origin thus facilitating identification and management of the underlying cancer.

Diagnosis is based on a combination detailed ophthalmological examinations, biological tests for specific autoantibodies, and targeted oncological investigations. The key to treatment lies in the management of the primary tumor, often combined with immunomodulatory therapies to limit autoimmune damage induced by the immune system's aberrant response.

This article reports four observations of patients with ocular involvement in paraneoplastic syndromes secondary to systemic cancers. Through these clinical cases, we highlight the underlying pathophysiological mechanisms, appropriate diagnostic and therapeutic strategies, and the importance of close collaboration between ophthalmologists, internists, geriatricians and oncologists to optimize the management of these patients.

CLINICAL CASES

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 haematuria. 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 tumour, 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, paresthesias of the upper limbs, feverish sensation and altered general condition consisting 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 an 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 anaemia 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 10aregenerative in the context of a myelodysplastic 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 on 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 presence monoclonal immunoglobulin 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 therapy was initiated to manage ocular manifestations, with a favorable outcome.

DISCUSSION

Paraneoplastic uveitis is a rare entity, but represents a diagnostic and therapeutic challenge due to its association with an often unrecognized underlying tumor process . They occur as part of an autoimmune response directed against tumor antigens expressed by both the tumor and ocular structures. This aberrant recognition by the immune system can manifest itself in different clinical forms, ranging from anterior uveitis to granulomatous panuveitis, as illustrated in the reported cases.

Pathophysiological mechanisms

Ophthalmic paraneoplastic syndromes are based on a phenomenon of molecular mimicry. Autoantibodies directed against tumor antigens can interact with proteins expressed in the eye, triggering an inflammatory reaction. This reaction may be enhanced by the presence of activated immune cells in the tumor environment, which induce systemic inflammation that can disrupt the blood-ocular barrier.

In CAR (cancer-associated retinopathy) and MAR (melanoma-associated retinopathy) , anti-retinal autoantibodies such as anti-recoverin or anti-ENOA have been identified. However, for uveitis associated with paraneoplastic syndromes, the mechanisms remain poorly defined, and appear to involve immune reactions directed against uveal pigment cells.

Differential diagnosis and diagnostic strategies

The identification of paraneoplastic uveitis is based on a range of clinical and paraclinical arguments. The diagnosis is made in the presence of atypical uveitis, resistant to conventional

treatments, associated with unexplained systemic symptoms (decline in general condition, altered nutritional status, arthralgias, inflammatory syndromes). The work-up should include :

• A full ophthalmological examination with fluorescein angiography and optical coherence tomography (OCT) to assess retinal and uveal damage.

• A search specific autoantibodies such as anti-recoverin, anti-CRMP-5, anti-amphiphysin.

• A targeted imaging based on symptoms (thoraco-abdomino-pelvic CT, brain MRI) to detect underlying cancer.

• Cerebrospinal fluid analysis for suspected paraneoplastic optic neuropathy.

The importance of the haematological work-up is highlighted in our cases, where plasma protein electrophoresis and myelograms were used identify monoclonal gammopathies associated with ocular damage.

Management and prognosis

The therapeutic strategy is based on management of the underlying cancer. Local or systemic corticosteroid therapy is often introduced to limit the inflammatory reaction and improve ocular symptomatology. However, a lasting response is rarely achieved without treating the primary tumor.

In reported cases :

• The patient with urothelial carcinoma showed improvement of his ocular involvement after RTUTV and intravesical BCG instillations.

• The multiple myeloma patient had required a VCD protocol, with stabilization of ophthalmological manifestations.

• The patient with MGUS had progressed favorably on corticosteroids and valaciclovir, with close hematological monitoring.

• The thyroid carcinoma had been treated with total thyroidectomy and radiotherapy, leading to regression of ophthalmological signs.

The prognosis of paraneoplastic uveitis is variable, and depends on both the evolution of the tumor pathology and the earliness of the diagnosis. Prolonged monitoring is recommended, as these patients are at risk tumor recurrence or evolution towards a 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.

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