Autoimmune retinitis: Report of three cases

Autoimmune retinitis: a propósito de 3 casos clínicos

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Abstract

Autoimmune retinitis comprises a spectrum of diseases that share clinical features and pathophysiology, which refers to the presence of retinal antibodies that produce panretinal degeneration. The clinical features are progressive and painless visual acuity loss associated with photopsia, entopsia and nyctalopia, with a normal fundus in many cases. The history of neoplastic disease is important regarding diagnosis, treatment and prognosis when suspecting this entity. It is necessary to rely on the Goldmann visual field, macular OCT, electroretinography and retinal antibodies to confirm the diagnosis. This disease represents a challenge for the ophthalmologist given the absence of standardized diagnostic criteria. The purpose of this paper is a brief review of the disease and describing three cases of autoimmune retinitis who attended the Andes Ophthalmological Foundation.

Key words: Autoimmune retinopathy. Cancer-associated retinopathy. Melanoma-associated retinopathy.

Resumen

La retinitis autoinmune comprende un espectro de enfermedades que comparten características clínicas, y cuya fisiopatología se centra en la presencia de anticuerpos retinales que producen degeneración panretinal. El cuadro clínico se caracteriza por pérdida de agudeza visual progresiva e indolora asociada a fotopsias, entopsia y nictalopía, siendo el fondo de ojo muchas veces de aspecto normal. El antecedente de enfermedad neoplásica cobra importancia en relación con el diagnóstico, tratamiento y pronóstico, al momento de sospechar esta entidad. Es necesario apoyarse en el campo visual de Goldmann, OCT de mácula, electroretinograma y anticuerpos retinales para confirmar el diagnóstico. Esta enfermedad representa un verdadero desafío para el oftalmólogo, dada la ausencia de criterios diagnósticos estandarizados. El propósito de este trabajo es describir 3 casos de retinitis autoinmune que consultaron en la Fundación Oftalmológica los Andes, y realizar una breve revisión de la enfermedad.

Palabras clave: Retinopatía autoinmune. Retinopatía asociada a cáncer. Retinopatía asociada a melanoma.

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Introduction

Autoimmune retinitis comprises a spectrum of diseases that includes: a) cancer-associated retinopathy; b) melanoma-associated retinopathy; c) non-paraneoplastic autoimmune retinopathy; and d) bilateral diffuse uveal melanocytic proliferation^{1,2}.

All these diseases have clinical and pathophysiological features in common, characterized by the presence of specific or cross-reactive antibodies against retinal antigens, causing damage at the level of photoreceptors, bipolar cells and ganglion cells. This determines a panretinal degeneration, mainly altering the function of the external retina¹. The presence of these antibodies is not necessary or sufficient for diagnosis, since they can be negative in patients who have the disease³ or detected in the plasma of healthy individuals^{1,4}.

The sharing of clinical characteristics with other degenerative disorders of the retina, having heterogeneous forms of presentation and being a rare disease, makes the diagnosis of autoimmune retinitis a true ophthalmological challenge in the absence of standardized diagnostic criteria.

The purpose of this article is to present three cases of autoimmune retinitis attended at Fundación Oftalmológica los Andes and to review the characteristics of the disease.

Case report 1

A 35-year-old female, with history of thyroid cancer who underwent surgery 6 months prior to consultation, without significant family history and no history of allergies or daily medication intake. She consults for progressive visual acuity decrease for almost a year, worse in the right eye, associated with nyctalopia and brief episodes of photopsia. She also refers subjective decrease of the visual field in the right eye.

Upon examination: normal intraocular pressure, corrected visual acuity in the right eye (OD) of 1.0 and 0.4 in the left eye (OS). Normal pupillary light reflex, without relative afferent pupillary defect. Biomicroscopy: clear cornea, deep anterior chamber, Tyndall (-), normal lens and iris in both eyes. Fundus with clear vitreous without cells, non-excavated discs with normal appearance, macula without alterations, periphery without lesions.

Previous exams of the patient show: Goldmann visual field (GVF) with ring scotoma in OD, normal in OS (Figs. 1A and B); OCT with parafoveal atrophy in OD and normal in OS, autofluorescence shows macular hyperfluorescent ring in OD and no alterations in OS (fig. 2).

A standard electroretinogram shows OD with no rod and cone response, with the maximum response severely diminished in amplitude, and OS with slight decrease in a-wave amplitude under scotopic conditions (figs. 3A-C). Negative anti-recoverin, anti-GAPDH, and anti-endolase antibodies with positive anti-enolase antibodies. A diagnosis of autoimmune retinitis associated with thyroid cancer was made. Later, a reduction in Goldmann visual field led to initiate therapy with corticosteroids and immunosuppressants (mycophenolate 8 mg/kg/day), achieving good visual acuity in the right eye.

Case report 2

Male 62-year-old patient, with history of controlled hypertension, taking losartan and acetylsalicylic acid. Without relevant family history, he attended our center due to a diagnosis of epiretinal membrane made by a specialist external to our Fundación. He had a 1-year non-painful progressive VA decrease associated with nyctalopia.

Ophthalmological examination showed a corrected VA of 0.4 in OD, 0.3 in OS and normal intraocular pressure. Examination revealed clear cornea and cataracts C2N02 (according to LOCS II classification) in both eyes. Fundus in both eyes showed normal retina and disc but with cellophane maculopathy associated with mild cystoid edema. Retinal periphery examination revealed no pigment or granulation, and retinal vessels were normal.

As part of previously performed tests, a macular OCT showed epiretinal membrane and macular edema in both eyes. The tests carried out in our center revealed macular edema by angiography, tubular visual field in both eyes, flat standard electroretinogram and negative anti-recoverin antibodies (other antibodies unavailable) in both eyes.

A presumed diagnosis of autoimmune retinitis was made and tests were requested to rule out neoplasia (chest, abdomen and pelvis scans and evaluation by dermatology) which were negative. Subtenonian corticosteroids were initiated with a VA improvement in OD to 0.5 and OS to 0.3.

Biomicroscopy and fundus remained unchanged. In subsequent consultations, OCT showed evidence of a decrease in macular edema and improved Goldmann visual fields, with a small temporal island in both eyes.

Case report 3

Fifty-four year-old female with history of rheumatoid arthritis and hypothyroidism under treatment, taking

Figure 1. Goldmann visual field. Case report 1.

Figure 2. Autofluorescence in both eyes. Case report 1.

hydroxychloroquine from 1993 to 2011 with a dose of 200 mg per day and without relevant family history. She consulted in 2013 for a 2-year history of mild visual acuity decrease in both eyes, worse in OD, with nyctalopia and subjective progressive decrease of the visual field, with occasional entopsia, without photopsia. Previously, another center examined the patient, and a suspicion of autoimmune retinitis led to test anti-recoverin antibodies that were negative. The decrease in VA was attributed to the administration of hydroxychloroquine, so it was discontinued immediately.

Examination showed normal intraocular pressure, corrected visual acuity of 0.9 in OD and 1.0 in OS, normal pupillary reflexes, without relative afferent pupillary defect. Biomicroscopy showed clear corneas, normal anterior chamber, Tyndall (-), normal lens and iris in both eyes. Fundus in both eyes revealed clear vitreous without cells, normal disc with a 0.45 excavation, retina without “bone spicule” formation, normal macula with preserved foveal reflex, subtle retinal atrophy around the arcades. The following tests were requested: Goldmann visual field (both eyes) that showed peripheral pericentral scotomas (figs. 4A and B), OCT that showed

Figure 3. Standard electroretinogram. Case report 1.

perifoveal atrophy in both eyes, with preservation of foveal thickness and OS with intra-retinal cysts. An angiography in OD showed an inferior window defect, OS with window defect and petaloid leakage pattern and

«starry sky»-like appearance in the periphery of both eyes. Standard ERG in both eyes was completely flat in all its sequences. Autofluorescence in both eyes showed hypofluorescence in the temporal arcades.

Figure 4. Goldmann visual field. Case report 3

Given this unclear picture, autoimmune retinitis vs acute zonal occult outer retinopathy were suspected, and complementary tests with other types of antibodies were requested, showing anti- α -enolase (+), anti-carbonic anhydrase type II (+), and anti-tubulin (+) antibodies. Thorax, abdomen and pelvis scans were negative, and the patient was referred to a dermatologist to exclude melanoma and to a rheumatologist to initiate immunosuppressive treatment.

Discussion

The cases described reflect the difficulty in the diagnostic process of this disease. Although there are no standardized diagnostic criteria, certain clinical characteristics lead the ophthalmologist to suspect this disease.

Autoimmune retinitis usually manifests, on average, during the 5th decade of life. In most cases, it presents as a sudden decrease in VA, which is rapidly progressive and painless and usually associated with photopsia and photosensitivity, among other symptoms⁵. Usually it is bilateral; however, it can occur asymmetrically and even unilaterally. Visual field loss extent and pattern is variable, ranging from a central or paracentral scotoma to peripheral visual field constriction. In other cases, it also manifests as a generalized loss of sensitivity⁶.

In the literature, the association between autoimmune retinitis and autoimmune and neoplastic diseases is widely described⁷. Among the latter, malignant melanoma (constituting one of the phenotypes of the disease), small-cell lung cancer and some gynecological cancers (cervical, endometrial and ovarian)⁷ are among the

most common. This is why this history should make the clinician suspect this disease and, vice versa, an associated neoplastic process must be ruled out after the diagnosis of autoimmune retinitis. Some series reveal that the diagnosis of neoplasia precedes that of autoimmune retinitis in half of the cases⁷.

Regarding clinical evaluation, the fundus at the time of presentation of the disease is usually normal, and it can remain normal or evolve towards retinal pigment epithelium atrophy, mottling and attenuation of the retinal vessels, thus simulating the appearance of some retinal dystrophies¹.

When evaluating the patient, standard electroretinogram is an essential component in the diagnosis, since it provides an objective evaluation of retinal function¹. In this disease, the electroretinogram typically shows a negative wave pattern, although some subtypes, such as cancer-associated retinopathy and non-paraneoplastic autoimmune retinopathy, present a pattern of cone dysfunction, mainly affecting the A wave². The negative wave pattern presents as well in other diseases such as central retinal artery occlusion, photoreceptor dystrophy and ocular siderosis⁸. Given the range of differential diagnoses, the clinical evaluation of the patient across its spectrum, coupled with complementary tests, are essential for the suspicion, diagnosis and early treatment of this disease.

Macular OCT shows several alterations of the external retina, like loss of the photoreceptor layer, disruption of the junction of the internal and external segments, loss of the external limiting membrane and thinning of both the outer nuclear layer and at the central macular level⁹⁻¹¹.

Autofluorescence may show early or late alterations, like a hyperfluorescent ring in the parafoveal region⁹⁻¹¹ that suggests a compromise of pigment epithelium function. As the disease progresses, panretinal degeneration and cystoid macular edema become evident⁹.

The demonstration of anti-retinal antibodies supports the diagnosis^{2,4,5}. The 2 most frequently associated antibodies are anti-recoverin and anti- α -enolase^{5,6}; however, the presence of these is not mandatory or sufficient, as they can be negative in patients who have the disease³, or positive in the plasma of healthy individuals^{1,4}. This makes us question the role of antibodies in the pathogenesis of the disease, and in turn the performance of these in the diagnosis. Seropositivity according to different series is between 41% and 65%, and is more frequent in cancer-associated autoimmune retinitis, where positivity is a visual prognostic factor¹². Even so, the lack of internationally accepted trials that explain the role of serology in the diagnosis of the disease does not allow clarifying the role of these agents, both in the pathophysiology and in the diagnosis of the disease.

It is important to mention that these antibodies may be positive in other diseases, such as retinitis pigmentosa, Vogt-Koyanagi-Harada disease, age-related macular degeneration and diabetic retinopathy¹³.

There are no defined protocols for the treatment of autoimmune retinitis, and evidence is based mainly on cases of paraneoplastic autoimmune retinopathy⁵. Most treatments aim to reduce the immune response and to achieve immunomodulation, so local corticosteroids, intravenous immunoglobulin, plasmapheresis and some antimetabolites such as mycophenolate, azathioprine and cyclosporine are used. Other therapies described include monoclonal antibodies such as rituximab (anti CD-20)⁵. Unfortunately, therapy is not useful once retinal degeneration has occurred, so early diagnosis is essential in these cases.

The visual prognosis of these patients in general is poor, reaching average visual acuities of 20/100 or worse when they are associated with the presence of anti- α -enolase antibodies in serum, and in general progressing to blindness when the disease is associated with anti-recoverin antibodies². However, reports indicate that patients with cancer-associated retinopathy who have positive anti-recoverin antibodies have a longer survival, probably due to increased T cell activity against the tumor².

Finally, the progression of the disease is uncertain, since although some of the patients remain stable even in the absence of treatment, others progress despite immunomodulatory therapy, so the role and benefit of the latter is not completely elucidated⁵.

Conclusion

The diagnosis of autoimmune retinitis represents a challenge even for an experienced clinician. Cases such as those previously described could help to perform trials with a greater number of patients to allow a better characterization and understanding of autoimmune retinitis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflicts of interest

The authors declare no conflicts of interest.

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