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(CASE REPORT)

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Adalimumab in Vogt-Koyanagi-Harada disease: Case report and literature review

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Abstract

Vogt-Koyanagi-Harada syndrome is a rare autoimmune disease primarily affecting pigmented tissues with frequent ocular complications. Early and aggressive control of intraocular inflammation is essential, typically involving corticosteroids and immunosuppressive agents.

Biologic therapies, especially adalimumab, have shown promise in refractory cases, supporting their use to prevent relapses and reduce corticosteroid dependence.

We report a clinical case about 13-year-old female, manifesting as sudden bilateral vision loss and ocular inflammation. Initial examination revealed significant visual impairment, bilateral conjunctival hyperemia, granulomatous panuveitis, and serous retinal detachments. Angiographic findings showed characteristic papillary edema and multiple subretinal exudative lesions. All systemic, infectious, and immunological investigations returned normal results, leading to a diagnosis of the "possible" ocular isolated form of VKH. Standard treatment with high-dose corticosteroids and azathioprine resulted in recurrent, steroid-dependent uveitis. Introduction of adalimumab biotherapy achieved complete functional recovery, restoring visual acuity to 10/10 in both eyes, resolving retinal detachments, and leaving only residual pigment epithelium alterations.

This case highlights the efficacy of TNF-alpha inhibitors in managing refractory ocular VKH and achieving corticosteroid sparing.

Keywords: Auto-immune disease**;** Vogt-koyanagi Harada; Ocular manifestation; Biotherapy; Adalimumab

1. Introduction

Vogt-Koyanagi-Harada (VKH) disease is a chronic bilateral granulomatous with ocular and extraocular involvement (central nervous system and auditory and integumentary findings). The ocular manifestations of the VKH syndrome are more constant (1) . This typically presents in the eye with acute findings of granulomatous anterior uveitis, diffuse choroidal thickening, multiple focal areas of sub-retinal fluid and, in severe cases, optic nerve involvement with bullous serous retinal detachment (2) . VKH disease presents clinically in 4 different phases: prodromal, acute inflammatory, chronic, and recurrent (3) and it's classified as complete, incomplete, or probable (4) . In its complete form, manifestations appear according to disease stage and skin pigmentation. Their order of appearance is usually neurological and auditory signs first, then ocular, and finally cutaneous signs (5). Both ocular inflammation and complications, including complicated cataract, secondary glaucoma, choroidal neovascularization and subretinal fibrosis, can result in severe vision loss. Basis of treatment is local and general. The present mainstay principle of treatment in VKH relies largely on early control of intraocular inflammation with systemic high-dose glucocorticoids

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and immunosuppressive agents (6) . Biotherapies are a new effective therapeutic approach. Through this clinical observation, we emphasize the interest of TNF alpha inhibitors in the treatment of uveitis during VKH syndrome to prevent relapses and ensure cortisonic sparing.

2. Patients and methods

A 13-year-old child with no particular pathological or traumatic history presents to the emergency room for a sudden bilateral decrease in visual acuity associated with eye redness without other extraocular signs. The visual acuity was 2/10 and 1/10 in the right and left eye respectively. At the level of both eyes, we found a conjunctival hyperemia with retrodesmetic precipitates in sheep fat, a tyndall 3 +++, iridocristalline synechiae, a clear lens with vitreous tyndall and at the fundus a papillary edema stage 2 and multiple extensive serous retinal detachment. Thus, the uveitis was classified as a non-hypertensive synechial granulomatous bilateral panuveitis.

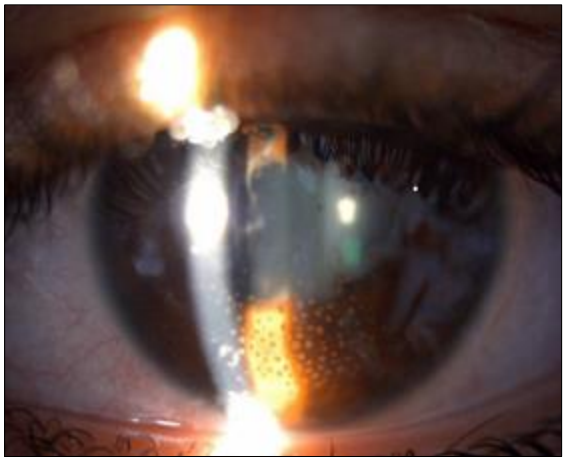

Figure 1 Non hypertensive synechial granulomatous panuveitis

The fluorescent angiography found a bilateral papillary oedema and multiple dots (pin point) increase in size gradually during the angiographic sequence associated with a heterogeneous aspect of choroidal fluorescence with at late time the confluence of these pin-points with accumulation of the dye in the subretinal space thus delimiting the multiple exudative retinal serous detachments.

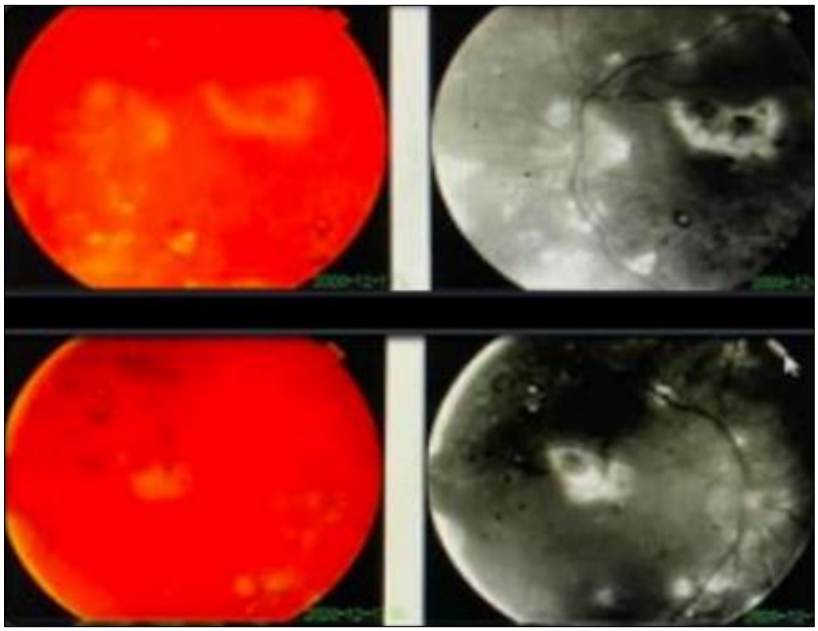

Figure 2 Fluorescent angiography: **B**ilateral papillary oedema and multiple dots

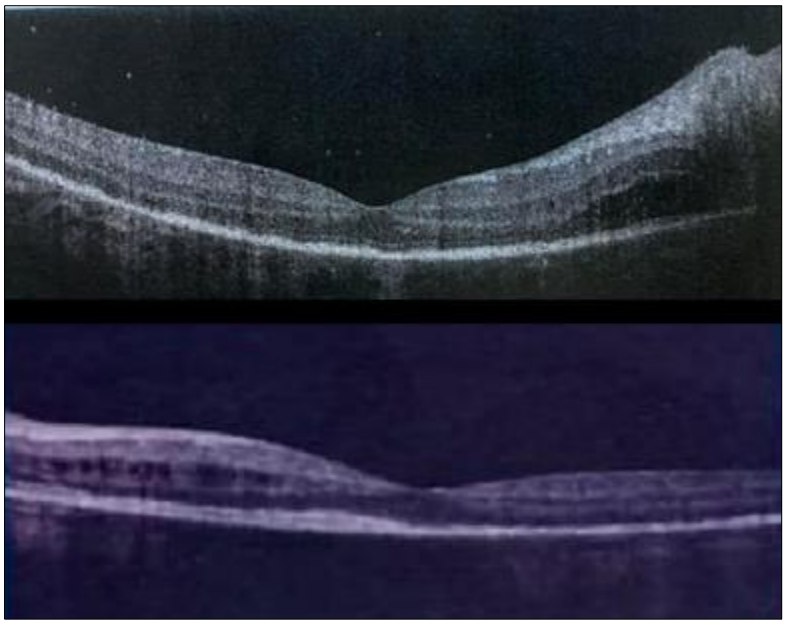

Figure 3 OCT: retinal serous detachment

The biological, radiological, infectious and immunological assessment performed returned normal. The diagnosis of VKH syndrome in its purely ocular form, so-called "possible" form was retained.

The therapeutic management was based on the administration of Methylprednisolone bolus of 1g/d for 3 days, Prednisone 1mg/kg/day and Azathioprine. The evolution was recurrent and corticosteroid-dependent uveitis at high doses. Thus, an initiation of biotherapy based on Adalimumab has been started followed by a good evolution that was marked by complete functional recovery with a visual acuity of 10/10 in both eyes with disappearance of serous retinal detachment on angiography and persistence of some hyperfluorescent areas corresponding to pigmentation disorder of the pigmentation of the pigment epithelium.

3. Discussion

Vogt-Koyanagi-Harada (VKH) disease is a rare, multisystem, autoimmune disorder with numerous clinical manifestations, in the eye, inner ear, central nervous system, hair and skin (7) in its complete form . It is an autoimmune inflammatory condition (3) .While the cause of VKH remains unknown, theories revolve around a cell mediated immune reaction acting against melanocytes, so that melanocytes present in any organ may be affected . This is also thought to be the reason why VKH typically affects darkly-pigmented races (5) .

VKH syndrome can be also incomplete, the latter being exclusively ocular such is our case. The ocular manifestations of the VKH syndrome are more constant and include iridocyclitis, vitritis, diffuse swelling of the choroid, serous retinal detachment, and optic disc hyperemia (1) . Procedures that may aid in the diagnosis include lumbar puncture, fluorescein angiography, and standardized echography (1). *D.J Forster and al* used in their study standardized echography (standardized A-scan and contact B-scan echography), at 9 patients with clear media and clinical evidence of VKH syndrome. Findings included :diffuse, low to medium reflective thickening of the choroid posteriorly; serous retinal detachment, located inferiorly or in the posterior pole; mild vitreous opacities with no posterior vitreous detachment; and thickening of the sclera and/or episclera posteriorly (8) . Fluorescein angiography and indocyanine green angiography demonstrate multiple choroidal lesions and serous retinal detachments in a patient with early-stage Vogt-Koyanagi-Harada disease (9).

For the optical coherence tomography (OCT) , it allows earlier diagnosis of VKH disease by revealing heterogeneous exudative detachments of the retina in the acute stage and choroidal thickening, and by demonstrating choroidal thinning in the chronic stage (3) . *Shizhao Yang and al* (6) have indicated in their study that treatment of VKH depends largely on early control of intraocular inflammation, and patients treated properly might have an optimistic prognosis for visual function. Unfortunately, many VKH patients do not receive proper treatment, instead receiving delayed or inadequate therapy (suboptimal medication, premature tapering of medication or absence of immunosuppressants),

and the disease inevitably progresses to the chronic recurrent stage, in which granulomatous ocular inflammation recurs and most ocular complications emerge, including complicated cataract, secondary glaucoma, choroidal neovascularization, subretinal fibrosis and others (3-4-5). *Pedro Arriola-Villalobos and al* (5) conducted a retrospective analysis of data from the medical records of patients with VKH who have been followed over the past 10 years at Spanish tertiary hospitals with specialized uveitis units . This study found that the most frequent complication in their population was cataract (41.1%), the second one was glaucoma (16.1%). Macular edema was the third most frequent complication (14.3%) which is the main cause of vision loss in uveitis and should be appropriately monitored and pupillary seclusion.

The conventional mainstay of treatment in VKH is combination therapy with systemic glucocorticoids and immunosuppressive agents, including cyclosporine, azathioprine and methotrexate. But sometimes other therapeutic remedies are used, especially in patients with chronic, recurrent or even refractory VKH exposing to intolerance and resistance to conventional treatments (6) . Systemic high-dose corticosteroids remain the first line treatment for VKH (13) and have been linked to reductions in recurrences and in the duration and total dose of maintenance corticosteroids. The initial treatment in most of *Pedro Arriola-Villalobos and al* 's study participants was oral corticosteroids given at a dose of 1 mg/kg/day (35.3%), followed by intravenous corticosteroids (250 mg/day to 1 g/day) (30.4%). These regimens are in line with those used in other population studies. Benefits have been reported of more than 6 months of immunosuppressive treatment (14) and the use of immunosuppressive therapy as first line treatment for disease control is indicated (15) as it avoids the secondary effects of long-term corticosteroids. In fact, nowadays a combination of steroidal and non-steroidal immunosuppression in the acute phase has been proposed to achieve better control of the uveitis, facilitating an earlier with drawal of corticosteroids and avoiding the appearance of manifestations of the chronic phase (16) .In the spanish study (5) , the most frequently used immunosuppressive drug was azathioprine (27.8%), followed by cyclosporine (24.1%). The percentage of biological agents used was 33.3%, the most employed being adalimumab (ADA) (22.2% of total, 66.6% of all biologics). As we know, TNF-α is regarded as a critical cytokine in the development of uveitis including VKH. ADA was the first anti-TNF-α antibody indicated for non-infectious uveitis by the FDA, the European Medicines Agency and the National Medical Products Administration (NMPA) of China (6) . *Kwon et al., Su et al. and Jeroudi et al*. reported that ADA effectively treated refractory VKH, preserving the patients' BCVA, deactivating ocular inflammation and reducing the daily prednisone dose. However, these studies were case reports with only 1 or 2 patients, and they focused mainly on pediatric patients (6) . *Cristobal an al* reported in their study of 14 patients with VKH , that the treatment with adalimumab is an effective and safe option, reducing the need for oral corticosteroid and conventional immunosuppressive therapy (17) . *Takayama and al* reported a case about a 66-year-old woman diagnosed with chronic VKH resistant to medications complicated by corticosteroid-induced CSC was made. Systemic corticosteroids and cyclosporine were tapered and adalimumab initiated. Bilateral ocular inflammation and CSC were gradually reduced and visual acuity improved without any adverse effect. Twelve months after starting adalimumab monotherapy, no signs of active VKH and CSC were present (18) . *Shunsaku Nakai and al* reported in a multicenter study that investigated efficacy and safety of adalimumab (ADA) treatment for exacerbation or recurrence of VKH patients with a medical records of 70 VKH patients who received ADA treatment for more than 6 months that ADA was shown to be effective to achieve remission of VKH disease refractory to conventional treatments and was generally well tolerated with few serious adverse events (19) .

4. Conclusion

VKH disease presents in its acute stage and incomplete form in most patients, with vision loss and serous retinal detachment as the most typical initial symptom and sign, and cataract as the most common complication. OCT and Fluorescent angiography should be considered an important diagnostic tool in VKH syndrome, standardized echography also especially when visualization of the fundus is poor or when clinical presentation is atypical. The disease has a good visual prognosis and patients can have good final visual outcomes if treated promptly and aggressively. The favorable visual outlook could be the outcome of aggressive corticosteroid treatment, which was the most employed initial treatment. In most patients, the initial regimen was switched to maintenance immunosuppressive therapy. Since its introduction, anti-TNF agents are increasingly becoming a popular choice of treatment for VKH as these have been shown to be safe and effective. However, more data is required to provide evidence that anti-TNF agents can be used as first-line treatment and as monotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict-of-interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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