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ORIGINAL ARTICLE

Bilateral Iris Depigmentation and Ocular Hypotony as End-Stage Manifestations of Untreated Vogt–Koyanagi–Harada Disease

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ABSTRACT

Purpose: To describe severe bilateral iris depigmentation and persistent ocular hypotony as end-stage manifestations of untreated Vogt–Koyanagi–Harada disease.

Methods: We present the clinical findings and diagnostic studies performed for three patients with bilateral iris depigmentation.

Results: Vogt–Koyanagi–Harada disease in late recurrent stage was diagnosed in three patients with bilateral severe iris depigmentation and persistent ocular hypotony.

Conclusions: Early diagnosis and treatment of inflammation are crucial factors in the clinical outcome of Vogt–Koyanagi–Harada disease. When left undiagnosed and untreated from early stages, severe iris depigmentation and ocular hypotony, uncommon manifestations of this disease, can develop.

Keywords: Iris atrophy, Iris depigmentation, ocular hypotony, panuveitis, Vogt–Koyanagi–Harada disease, VKH

Vogt–Koyanagi–Harada (VKH) disease affects pigmented tissues throughout the body, including the eyes, the meninges, the skin and the ears.[1,2] VKH presents clinically in four different stages: prodromal, uveitic, convalescent, and recurrent.[3]

Late manifestations of VKH include the following: ocular depigmentation that is clinically evidenced as Sunset-glow fundus and Sugiura sign; other ocular signs as nummular chorioretinal depigmented scars, retinal pigment epithelium clumping and/or migration and recurrent or chronic anterior uveitis; neurological and auditory findings as meningismus, headache, tinnitus, and pleocytosis (that could have resolved by the time of ophthalmic examination); and integumentary findings including alopecia, poliosis, and vitiligo.[1,3,4]

Of these manifestations, the most frequent is the Sunset-glow fundus. This finding was observed in almost all of the patients with recurrent uveitis attacks in a study on 410 VKH patients.[5]

We report three patients presenting with severe bilateral iris depigmentation and persistent ocular hypotony. These patients were not previously diagnosed nor treated for VKH disease. Further examination confirmed the diagnosis of VKH in late recurrent stage. The clinical manifestations reported in these cases are uncommon for VKH and are not frequently reported in the literature. To our knowledge, there are only three previous similar cases reported.[6–8]

CASE REPORTS

Case Report 1

70-year-old female referred to our service with a history of uveitis of 6 years of evolution with progressive visual acuity (VA) loss in both eyes. She had been treated earlier with intravitreal dexamethasone

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implant in her left eye (OS) and multiple doses of anti-angiogenic intravitreal therapy in both eyes for macular edema. She also had undergone intraocular lens (IOL) implantation and vitrectomy in both eyes due to cataracts and vitreous opacities. On admission, best-corrected visual acuity (BCVA) was 20/400 OD and count fingers at 3-feet OS. Her intraocular pressure (IOP) was within the 2–6 mmHg range in both eyes at three independent visits. Slit-lamp examination of both eyes revealed a clear cornea without keratic precipitates, anterior chamber with 0,5+ cells and a 3+ flare and iris with severe stromal atrophy (Figure 1) that became more evident under transillumination (Figure 2). Additionally, an IOL in the sulcus OD and in the capsular bag OS were observed. Fundus examination revealed no vitreous opacities, healthy optic nerves and "sunset glow" fundus.

Optical coherence tomography (OCT) (Figure 3A) and fluorescein angiography evidenced cystoid macular edema (CME) in both eyes. Furthermore, an ultrasound biomicroscopy (UBM) ruled out detachment of the ciliary body as responsible for the observed hypotony (Figure 3B) and enhanced depth imaging optical coherence tomography (EDI–OCT) ruled out choroidal thickening.

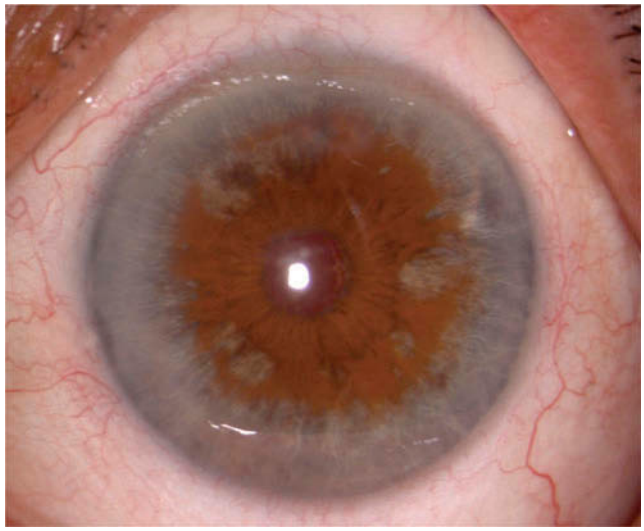

FIGURE 1. OS. Slit-lamp photography showing severe iris stromal atrophy with peripheral depigmentation.

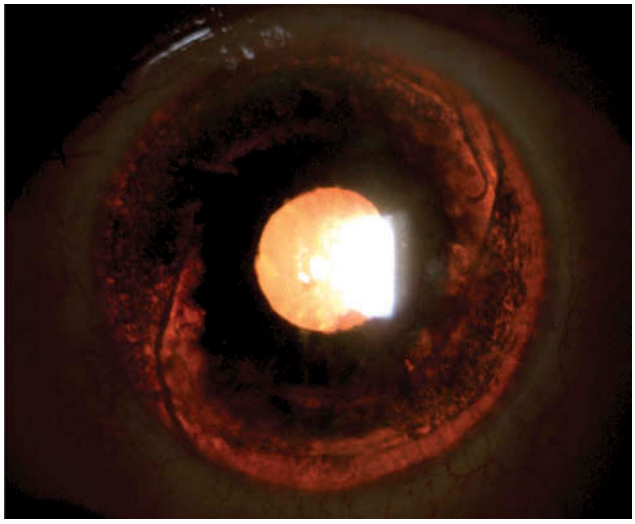

FIGURE 2. OS. Slit-lamp photography showing severe iris transillumination.

The patient did not show any depigmentation lesions in skin or annexes. Therefore, due to the ocular findings, she was diagnosed with bilateral panuveitis sequelae resulting from probable VKH in late recurrent stage. She was referred to rheumatology, and started on oral cyclosporine up to 5mg/kg per day. After six months of treatment the patient remained the same BCVA in both eyes, anterior chamber cells disappeared but 3+ flare was still present. Iris atrophy and ocular hypotony did not change or improve with the systemic immunosuppressive therapy.

Case Report II

This 34-year-old female was referred for a uveitis consultation due to a bilateral decrease in VA and floaters of one-year duration. She had a history of vitiligo lesions on eyelids, neck, arms and hands that

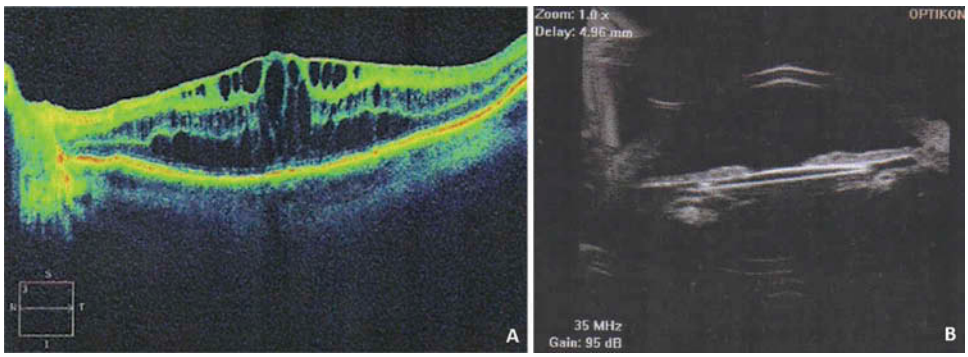

FIGURE 3. (A) OS. OCT that demonstrates cystoid macular edema. (B) OS. UBM that ruled out detachment of the ciliary body.

had appeared 3 years ago. Ophthalmic exam revealed BCVA of 20/25 OD and 20/60 OS. On slit-lamp examination of both eyes, the cornea had keratic precipitates, the anterior chamber had 0,5+ cells, there were focal areas of peripheral iris atrophy, and there was 360° posterior synechiae. (Figure 4) Cataracts were also noted in both eyes. Fundus examination was very limited due to bad pupil dilation and media opacities but the areas of retina observed had a reddish appearance. IOP was initially normal in both eyes, but in one of the controls OD was found to have ocular hypertension reaching up to 29 mmHg, which responded well to topical treatment. During the controls, when inflammation was controlled, IOP reached lower values between 4 to 6 mmHg OU. Systemic blood tests for infectious and rheumatologic diseases were negative. OCT was not possible due to lens opacity, UBM ruled out detachment of the ciliary body and B-scan ultrasound revealed bilateral choroidal thickening. (Figures 5A and 5B)

Based on ocular and dermatologic findings, she was diagnosed with incomplete VKH in late recurrent stage. Treatment with oral prednisone 1mg/kg, methotrexate escalating doses from 7.5 mg to 25 mg once weekly, and folic acid 1 mg/day was initiated achieving control of the inflammation in the anterior segment after 3 months, but with evidence of retinochoroidal thickening even after 15 months of treatment. Due to hypotony, it has not been possible to schedule the patient for cataract surgery until the present moment.

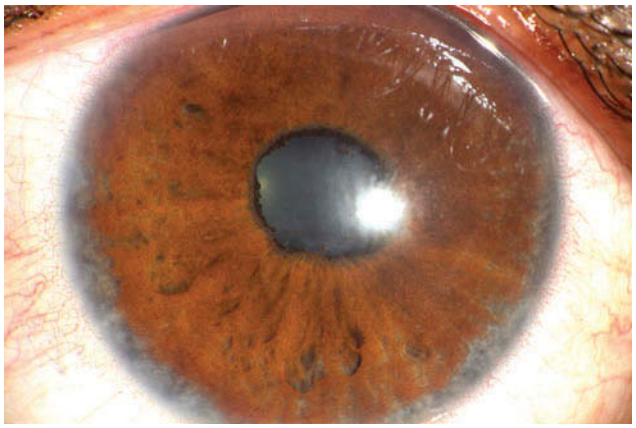

FIGURE 4. OD. Slit-lamp photography showing peripheral iris atrophy with depigmentation and 360° posterior synechiae.

Case Report III

This 61-year-old male was referred to our clinic for bilateral uveitis. He reported a decrease in VA in both eyes that did not improve with glasses and episodic red eyes of 3 years of evolution. On ophthalmic exam, we found BCVA of hand motion OD and 20/40 OS. On slit-lamp examination, OD was found to have a nasal pterygium, a cornea with granulomatous keratic precipitates, anterior chamber with no cells and 3+ flare, iris with secluded pupil and peripheral atrophy, and the fundus could not be evaluated because of the dense cataract (Figures 6 and 7); OS had a clear cornea, anterior chamber with no cells and 1+ flare, iris with posterior synechiae and peripheral atrophy, clear lens, and the fundus presented some peripheral choroidal inactive lesions and had a reddish appearance compatible with "sunset glow" fundus. IOP was 4mmHg OD and 8mmHg OS. Systemic examination revealed hypochromic lesions in the periocular area and vitiligo lesions on the hands (Figure 8). UBM ruled out detachment of the ciliary body as responsible for the observed hypotony and B-scan ultrasound revealed choroidal thickening in both eyes. (Figures 9A and 9B). Based on ocular and dermatologic findings, he was diagnosed with incomplete VKH in late recurrent stage. The patient underwent cataract surgery with IOL implantation in the right eye showing an improvement of his VA to 20/100. After surgery, sunset-glow fundus, peripheral choroidal inactive lesions and macular thickening were observed. Furthermore, OCT revealed CME with serous retinal detachment (Figure 9C), so the patient was scheduled for intravitreal dexamethasone implant.

DISCUSSION

Iris depigmentation and ocular hypotony are manifestations rarely seen and not often described in the

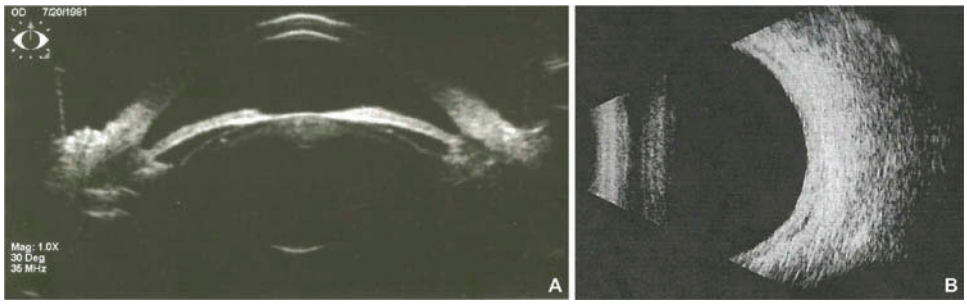

FIGURE 5. (A) OD. UBM ruled out detachment of the ciliary body. (B) OD. B-scan ultrasound revealed choroidal thickening.

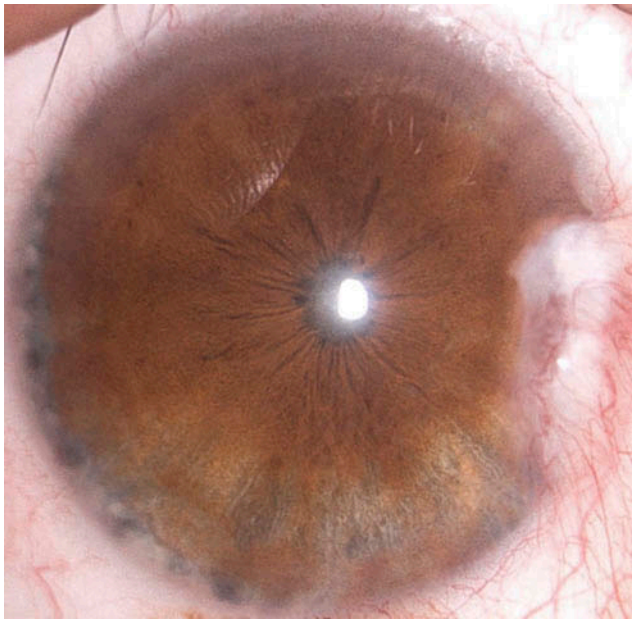

FIGURE 6. OD. Slit-lamp photography showing nasal pterygium, secluded pupil and areas of peripheral iris atrophy.

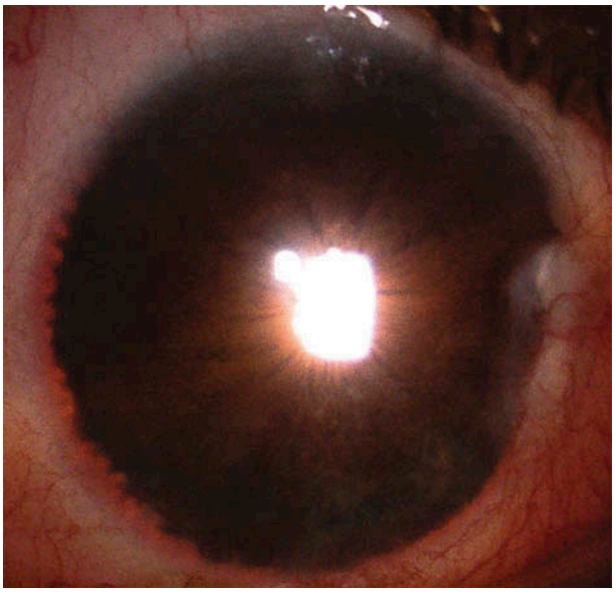

FIGURE 7. OD. Slit-lamp photography showing transillumination of peripheral iris atrophy.

literature of VKH disease in the late stage. In 2002, Suhler et al. described for the first time a case of peripheral iris depigmentation in a 13-year-old Israeli patient with incomplete VKH disease.[6] Subsequently, Saary and Nummelin,[7] and Attia et al[8] reported two additional cases of iris depigmentation and ocular hypotony in complete VKH patients. Interestingly, a common feature among these three cases was the lack of treatment with oral

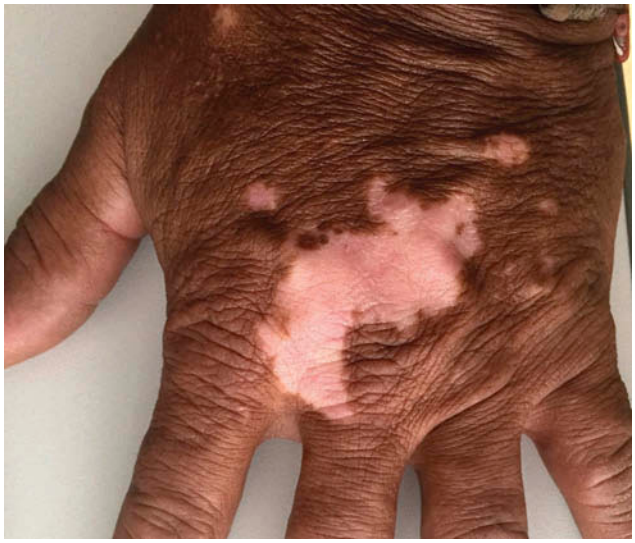

FIGURE 8. Hypochromic lesion compatible with vitiligo.

steroids or immunosuppressants during the acute phase of the disease.

To date, our report adds three additional patients presenting with iris depigmentation due to VKH disease, and to our knowledge is the first report of these findings in Latin American patients.

While the current classification of VKH disease as complete, incomplete or probable, takes into account the multi-systemic nature of this disease, additional considerations should be taken in order to include those cases of VKH with findings limited to the eyes, as it is an entity found more frequently than previously estimated.[9] In fact, a retrospective study has recently validated the clinical finding of sunset-glow fundus alone as having the highest positive predictive value (PPV = 94.5) in the diagnosis of VKH disease, and that this predictive value is not further increased by taking into consideration extraocular findings.[4]

According to the diagnostic criteria for VKH disease,[10] these cases correspond to a probable VKH disease for case I and incomplete VKH disease for cases II and III since case I had just ocular involvement and cases II and III had ocular and dermatologic findings compatible with the disease. Because of the advanced stage of the disease, the detection of neurologic and auditory symptoms were limited as these manifestations are characteristic of the prodromic and the uveitic stages.[1,3]

Interestingly, case I classified as probable VKH, presented the lowest levels of IOP and the greater iris depigmentation when comparing with cases II and III that were classified as incomplete VKH. The evolution time of the disease was longer in case I (6 years) than in cases II (1 year) and III (3 years), this could be related with the higher grade of iris depigmentation in case I.

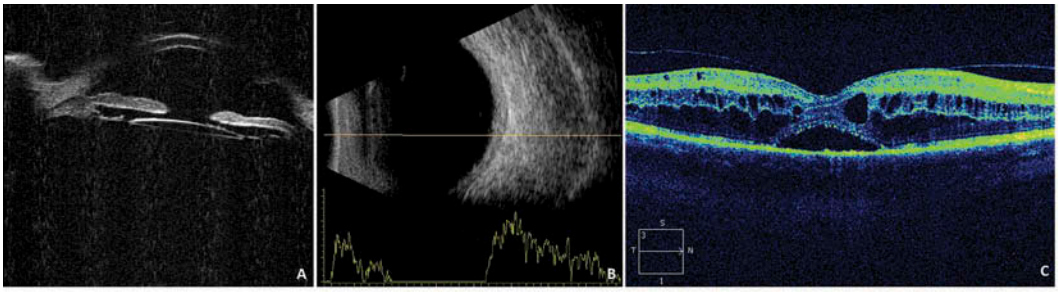

FIGURE 9. (A) OD. UBM ruled out detachment of the ciliary body. (B) OD. B-scan ultrasound revealed choroidal thickening. (C) OD. OCT revealed CME and serous retinal detachment.

It has been postulated that mean IOP measurements increased with increasing grades of iris pigmentation. A modest but statistically significant association between increasing iris color and IOP has been described, but the underlying pathogenesis of this relationship is not known.[11] Interestingly, in our cases the mean IOP measurements decreased with decreasing grades of iris pigmentation.

Differences in the three cases in the IOP, even in different eyes of the same case, could be explained by diverse factors such as the inflammation degree range in the anterior chamber, iris posterior synechiae, detachment of ciliary body or choroid. However, there were no major differences in the clinical presentation of the mentioned factors except for the presence of posterior synechiae. Lower IOP values were present in case I, in whom we did not find posterior synechiae contrary to case II and III in whom posterior synechiae were present.

Ocular hypotony could be associated with severe and chronic uncontrolled inflammation and both are mechanisms of suspected choroidal thickening.[12] In cases II and III, choroidal thickening was confirmed by ocular ultrasound.

On the other hand, retinal serous detachment of the posterior pole and serous detachment of the ciliary body are other mechanisms causing hypotony. In our cases, UBM ruled out detachment of the ciliary body in all cases and serous retinal detachment was documented only in Case I.

In our patients, the explanation for the iris stromal and pigment-epithelial depigmentation might be related to the hypothesis that liberated melanocytic cellular antigens specifically tyrosinase family proteins induce systemic autoimmunity and autoreactive lymphocytes against these proteins, producing the loss of color in areas containing pigment such us iris, skin and choroid.[13,14]

The fact that iris depigmentation is unusual, while cutaneous and choroid compromise are common in VKH patients, is not well determined. It is probably due to the presence of autoreactive T cells that cause damage in the iris stromal and pigment-epithelium only in chronic untreated cases.[15]

Timely treatment of VKH disease with steroids during the uveitic stage is of paramount importance as it may lessen the severity and evolution of the clinical manifestations in the late stages. A recent consensus, mentioned that even the Sunset-glow fundus, the most common late-stage finding, can be prevented by early and adequate treatment[16] and multiple studies have highlighted the importance of treatment during initial stages as it may avoid late-stage complications and reduce the recurrence frequency during the chronic phases.[16–18]

We report three VKH previously undiagnosed cases that, similarly to the three previous reports, did not receive systemic anti-inflammatory therapy during the initial stages. This therefore, leads us to conclude that bilateral iris depigmentation and ocular hypotony are clinical manifestations of severe and end-stage disease that may be accompanied by chronic complications like cataract, posterior synechiae and CME. The systemic immunosuppressive therapy started at this point of the disease did not improve the mentioned clinical findings.

In conclusion, our report illustrates the evolution of VKH disease in untreated patients, with an uncommon presentation of severe iris depigmentation accompanied by hypotony, and highlights the importance of acute systemic anti-inflammatory treatment in VKH disease.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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