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Azathioprine During the First Trimester of Pregnancy in a Patient with Vogt-Koyanagi-Harada Disease: A Multimodal Imaging Follow-Up Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Mariana Ingolotti
AEF 2 Bernardo A. Schlaen
DE 1,3 Enrique Alfonso Roig Melo-Granados
DE 3 Humberto Ruiz García
ABCDEF 3 Jorge Arturo Aguilera Partida

1 Department of Ophthalmology, Hospital Civil Fray Antonio Alcalde, Guadalajara, Jalisco, México
2 Department of Ophthalmology, Hospital Universitario Austral, Buenos Aires, Argentina
3 Clínica Oftalmológica (Ophthalmological Clinic) Santa Lucía, Guadalajara, Jalisco, México

Corresponding Author: Mariana Ingolotti, e-mail: m.ingolotti@gmail.com
Conflict of interest: None declared

Patient: Female, 27
Final Diagnosis: Vogt Koyanagi Harada Disease
Symptoms: Headache • vision loss
Medication: —
Clinical Procedure: —
Specialty: Ophthalmology

Objective: Unusual clinical course

Background: The aim of this study was to describe the case of a 27-year-old woman who developed Vogt-Koyanagi-Harada (VKH) disease in the 13th week of pregnancy, who was treated with high-dose oral corticosteroids and azathioprine due to its persistent course.

Case Report: A 27-year-old East Indian woman in her 13th week of pregnancy presented with bilateral decreased visual acuity and metamorphopsia due to bilateral serous retinal detachments and was diagnosed with Vogt-Koyanagi-Harada (VKH) disease. Multimodal imaging, including blue light fundus autofluorescence (FAF), structural spectral domain optical coherence tomography (SD-OCT), *en-face* OCT, and OCT angiography (OCT-A), was performed at presentation and follow-up, being particularly helpful for identifying recurrences. Her treatment consisted of high-dose corticosteroid therapy, and azathioprine had to be added as an adjuvant due to the aggressive behavior of the disease. She gave birth to a healthy baby at 31 weeks of gestation and remained with 20/20 vision at 8 weeks postpartum.

Conclusions: To the best of our knowledge, this is the first report on the use of azathioprine in VKH disease during pregnancy with a successful outcome. Multimodal imaging avoiding the use of fundus fluorescein angiography is key in the diagnosis and follow-up of VKH disease in pregnant women.

MeSH Keywords: Azathioprine • Pregnancy Complications • Tomography, Optical Coherence • Uveomeningoencephalitic Syndrome

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Background

Vogt-Koyanagi-Harada (VKH) disease is a systemic autoimmune disorder that affects melanocytes. The disease manifestations can be divided into 4 stages: prodromal, acute uveitic, chronic, and chronic recurrent. In its acute stage it is characterized by bilateral panuveitis with serous retinal detachment, as well as auditory and neurological symptoms. However, in its chronic stage the disease manifestations include chronic anterior uveitis, and integumentary and uveal depigmentation [1]. Interestingly, the clinical course of VKH is modified by pregnancy, with milder inflammatory manifestations during the second and third trimesters. Treatment of non-infectious uveitis during pregnancy is challenging, leading the physician to offer alternative options that present the least possible risk to the patient and fetus [2,3].

Non-invasive multimodal imaging studies are important complements for the diagnosis and follow-up of VKH disease.

In the present case report, we describe the case of young healthy woman who developed VKH disease during the 13th week of pregnancy, who was treated successfully with systemic corticosteroids and azathioprine. During her follow-up, we performed multimodal imaging, including blue light fundus autofluorescence (FAF), structural spectral domain optical coherence tomography (SD-OCT), enhanced deep imaging optical coherence tomography (EDI-OCT), and optical coherence tomography angiography (OCT-A).

Case Report

A 27-year-old East Indian female patient in her 13th week of pregnancy visited our institution due to bilateral decreased visual acuity and metamorphopsia beginning 15 days before. The patient had no previous history of any medical disorders, including hypertension. Her previous pregnancy was uneventful. At initial examination, her best-corrected visual acuity (BCVA) was 20/70 in the right eye and CF (count fingers) in the left eye. During slit lamp examination, mild anterior chamber inflammation (1+ cell, 1+ flare) was observed in both eyes. Intraocular pressure was 12 mmHg in both eyes. A funduscopic exam showed bilateral lobulated serous retinal detachments and optic nerve hyperemia (Figure 1A, 1B). In both eyes, FAF revealed a stippled perifoveal hypoautofluorescence (hypoAF), and hyperautofluorescence (hyperAF) at the borders

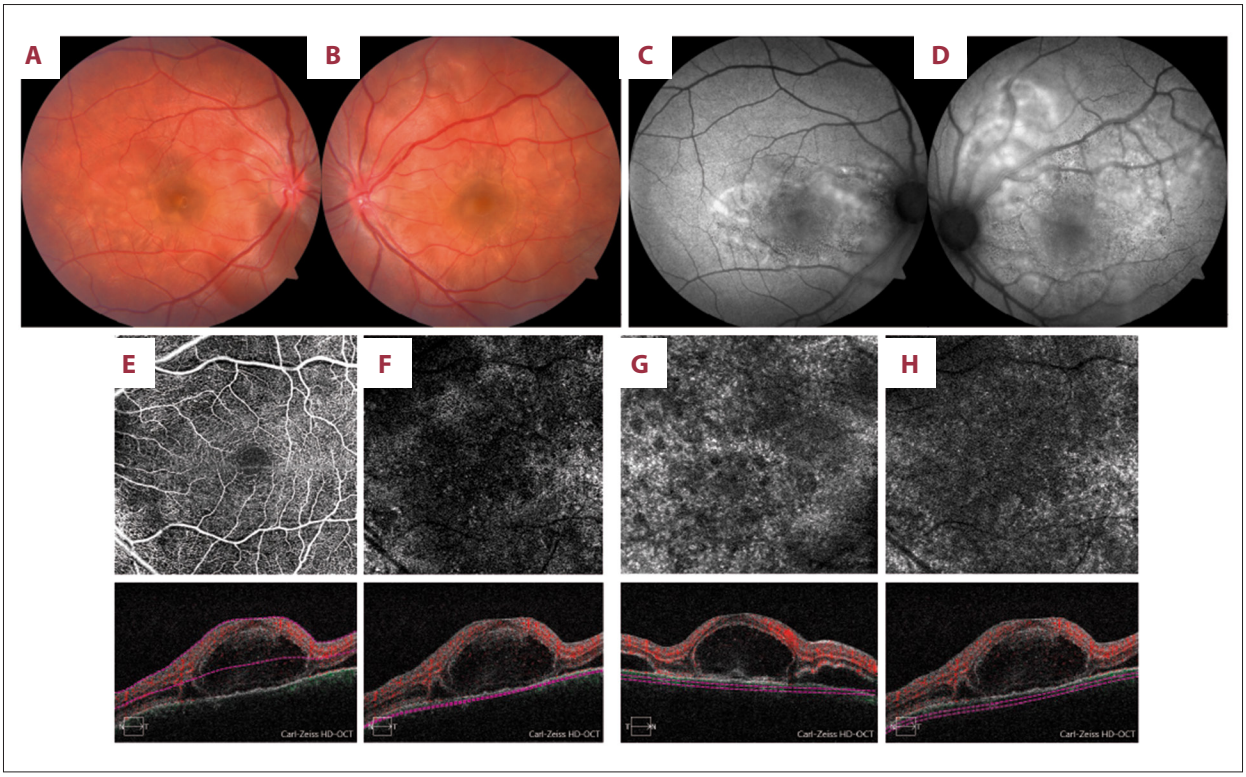

Figure 1. Multimodal exam at presentation. (**A, B**) Color fundus image with blurry and hyperemic optic nerve, choroiditis, and multiple serous detachments. (**C, D**) FAF showing stippled perifoveal hypoautofluorescence corresponding to the serous detachments and hyperautofluorescence at the borders with granular RPE pattern. (**E**) OCT-A of superficial capillary plexus of left eye showing no apparent flow impairment. (**F–H**) OCT-A of choriocapillaris of left eye and choroid of both eyes demonstrating relative hypo-flow areas.

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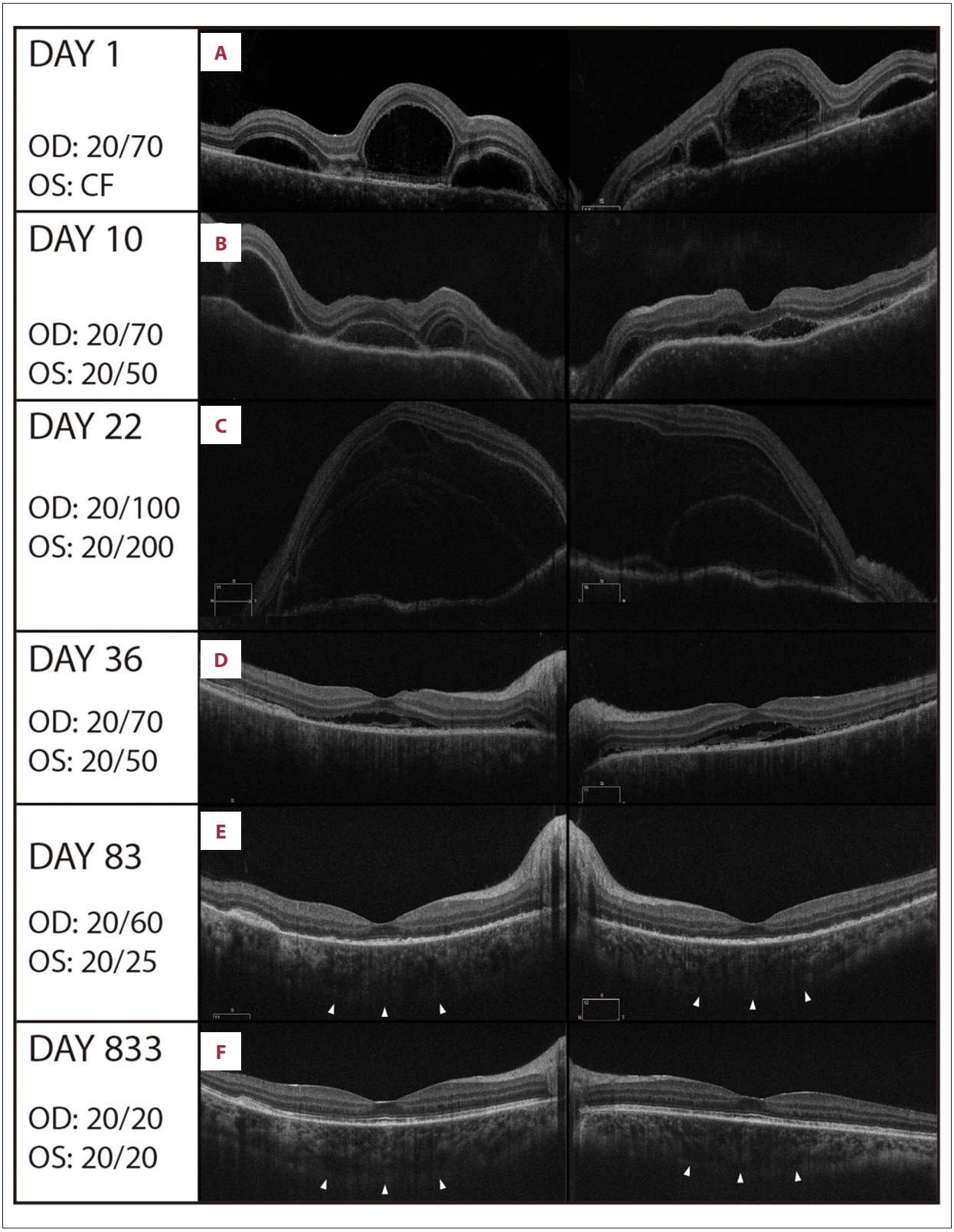

Figure 2. (A–F) SD-OCT changes during follow-up with corresponding BCVA.

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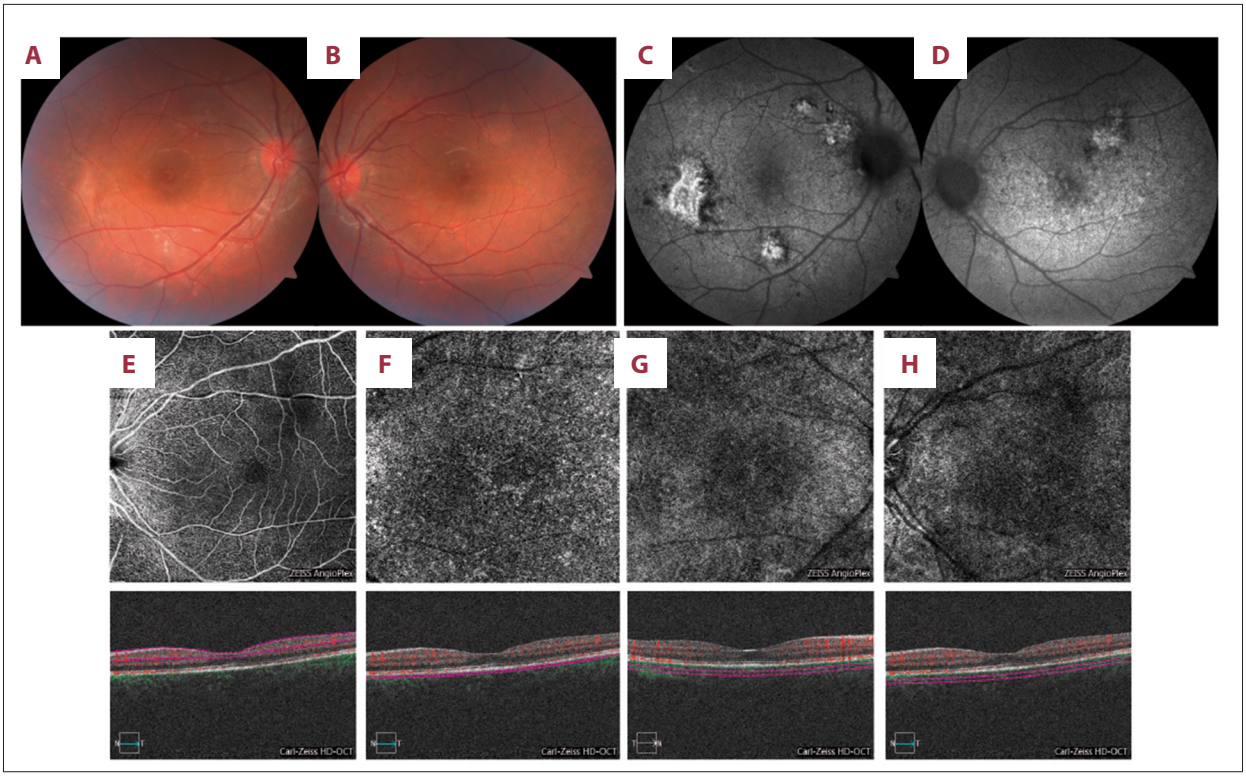

Figure 3. Multimodal exam at last follow-up. (**A, B**) Color fundus image with persistent hyperemic optic nerve and areas of subretinal fibrosis. (**C, D**) FAF showing hyperautofluorescence. (**E**) OCT-A of non-pathologic superficial capillary plexus left eye. (**F–H**) OCT-A of choriocapillaris left eye and choroid both eyes showing apparent restoration of flow.

of the serous detachments. In some of the serous detachments, the center was hypoautofluorescent (Figure 1C, 1D). SD-OCT (Carl Zeiss Meditec, Dublin, CA) showed bilateral serous retinal detachments separated by septa, intraretinal cysts, RPE undulations, and significant choroidal thickening (Figure 2A). OCT-A demonstrated normal superficial capillary plexi (Figure 1E), but there were multiple dark foci in the choriocapillaris and choroidal layer (Figure 1F–1H) due to a relatively decreased flow that co-localized with areas of increased choroidal thickness and hyporreflectivity in EDI-OCT.

She was diagnosed with VKH disease. Transeptal injection of 8 mg dexamethasone 21-isonicotinate (ALIN® Depot) was performed, followed by pulsed steroid treatment consisting of 1 g intravenous methylprednisolone daily for 3 days, followed by 50 mg oral prednisone combined with magaldrate/dimethicone for gastric protection.

At 10-day follow-up, she reported visual improvement in both eyes, reaching 20/70 and 20/50 visual acuity added to reduction of serous detachments on SD-OCT (Figure 2B). At 22-day follow-up, while she was on 40 mg prednisone daily, her vision decreased to 0.2 LogMAR (20/100) and 0.1 LogMAR (20/200) accompanied by 3+ cells in the anterior chamber, worsening of the serous detachments on SD-OCT (Figure 2C), and headache. After a new trans-septal injection of 8 mg dexamethasone 21-isonicotinate (ALIN® Depot), azathioprine 150 mg was added to the treatment, showing significant improvement at days 29 and 36 of follow-up (Figure 2D). Routine fetal ultrasound exams were performed for screening of any adverse effects of the drug, such as malformations, impaired fetal growth, and fetal distress. No adverse effects were found.

Unexpectedly, at day 83 of follow-up, she had a recurrence (Figure 2E) marked by headache, deafness, and progressive vision loss, which were attributed to the patient tapering (prednisone 5 mg and azathioprine 100 mg) the prescribed treatment without medical guidance. By that time, she was also on metformin due to hyperglycemia. Treatment was reinitiated with prednisone 30 mg and azathioprine 200 mg. By day 141, her visual acuity was 20/25 in both eyes, with complete resolution of the serous detachments. Nevertheless, her eyes showed marked pathologic changes confirmed by subretinal fibrosis, RPE changes, and sunset glow fundus (Figure 3A–3D). Additionally, her OCT-A exams revealed an apparent choriocapillaris and choroidal flow restoration (Figure 3E–3H).

Eventually, she had a caesarean section performed at week 31 of pregnancy due to cholestasis with hyperbilirubinemia and no hepatotoxicity, which was diagnosed as cholestasis of

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pregnancy, an entity not related to the medication she was on. Her baby was healthy, weighing 1900 g. No other adverse effects were observed at 8 weeks postpartum. The patient was continued on azathioprine 150 mg/day and prednisone 7.5 mg/day. At day 833 of final follow-up, her examination and SD-OCT exams did not show signs of active inflammation (Figure 2F). She remained with 20/20 vision in both eyes with no treatment and returned to her home country for further follow-up.

Discussion

In spite of being previously reported on several occasions [2–5], at the moment there is no standardized protocol for the treatment of Vogt-Koyanagi-Harada (VKH) disease during pregnancy.

Pregnancy entails a peculiar immunological state in which cellular response is suppressed, cytokine counts are lowered, and corticosteroid production boosted; subsequently, chronic inflammation of autoimmune diseases is attenuated [2].

According to several reports, an early aggressive treatment based on corticosteroids at high dosage, either intravenous or oral, is recommended and has proven effective to reduce the number of recurrences as well as convalescent signs and complications [6]. Studies using Swept Source Optical Coherence Tomography have demonstrated anatomical choroidal remodeling and consistent retinal changes after the use of systemic corticosteroid therapy [7]. In some cases, observation is the preferred option due to the mothers' refusal of treatment [8].

It has been proven that other immunosuppressive drugs such as cyclophosphamide [9], methotrexate [10], and mycophenolate mofetil [11] should be avoided in pregnancy. Conversely, azathioprine seems to be a safe immunosuppressant drug for these patients [12]. In the present case, azathioprine was shown to be well tolerated and safe for treating this young pregnant patient with VKH disease.

Azathioprine, a purine analog and prodrug of 6-mercaptuprine, is a well-known drug used for more than 50 years. Its main action is interfering with the DNA synthesis of rapidly dividing cells like T-lymphocytes. This results in immunosuppressive, cytotoxic, and anti-inflammatory effects according to the used dose [13]. Although studies in mice, rabbits, rats, and hamsters have shown teratogenic effects in their offspring, differences were found compared to human treatment regarding dose, drug exposure, and delivery [13].

Azathioprine has been used in various autoimmune diseases during pregnancy and puerperium, such as systemic lupus erythematosus [12], Crohn's disease [14], and autoimmune hepatitis [15]. Angelberger et al. reported that azathioprine did not seem to increase the risk of infections in babies exposed in utero and via breast-feeding. The most common adverse effects related to azathioprine are nausea, abdominal discomfort, and bone marrow suppression. The incidence of hepatotoxicity has been reported to range from 0% to 13% [16]. Our patient developed cholestasis during her third trimester of pregnancy, with no alteration of liver function or elevated liver enzymes, which resolved in the postpartum period with no need of azathioprine discontinuation.

Pregnancy also involves a diagnostic challenge due to women refusing to undergo invasive diagnostic exams such as fundus fluorescein angiography (FFA). Multimodality plays a key role in this situation. Autofluorescence findings in VKH disease enables physicians to assess RPE metabolic and functional stress. At early stages, hypoautofluorescence typically occurs because the signal is blocked by the serous retinal detachment. However, our patient presented hyperAF in relation to the serous detachments, possibly due to acute RPE distress [17]. In addition, targeted lesions consisting of hypoAF dots surrounded by a relative hyperAF halo have also been described as inverted images of what can be seen in the FFA [18].

OCT has allowed a broader understanding of the extent of the retinal and RPE damage [19]. Different findings have been described in the acute phase, such as areas of subretinal fluid accumulation, pigment epithelial detachment or undulations, subretinal septae, and choroidal folds. Enhanced Depth Imaging (EDI) OCT has added more information on choroidal thickness changes in each phase of the disease and has been proposed as a useful tool for follow-up [20]. Evident increase in choroidal thickness is seen in the acute phase, probably as a result of inflammatory infiltration and exudation. In some cases, the thickness increase goes beyond the limits of SD-OCT measurement range, as in our case, in which choroid could not be measured at presentation. Recurrences are also distinct due to rebound of the choroidal thickening, even without any other sign of reactivation of the disease [21]. On the contrary, during the chronic convalescent phase, the choroid has been found to be thinner and correlated to sunset glow fundus appearance [21].

A more recent non-invasive technology, the OCTA, has facilitated localizing ischemic damage in VKH disease due to its ability to explore deep retinochoroidal slabs. Although superficial and deep retinal capillary plexi are generally not affected, the images can seem pathologic due to false-positive artifacts caused by serous detachments, as seen in the present case. The main OCTA finding is located at the choriocapillaris layer, where dark irregular areas can be interpreted as signs of hypoperfusion [22]. Recently, focal areas of hypoperfusion in Sattler´s layer have been described as co-localizing to hypocyanescent areas seen in indocyanine green angiography (ICGA), suggesting that images might represent choroidal

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granulomas [23]. This last finding introduces another potential monitoring tool for VKH disease.

AF, SD-OCT, and OCTA have proven to be a useful in all steps. In our opinion, the inability to perform FFA was not an impediment to diagnosis or follow-up in our case.

Conclusions

VKH diagnosis and management during pregnancy are challenging. OCT-A can provide a comprehensive overview of retinal vasculature. In addition, it is a promising imaging modality for monitoring choroidal inflammatory involvement in pregnant women. Treatment should be tailored to every patient based on her needs. High-dose corticosteroid therapy remains the initial treatment of choice, but in non-responsive aggressive cases, adjuvant drugs such as azathioprine should be considered. To the best of our knowledge, this is the first report of the use of azathioprine in VKH disease during pregnancy.

Conflict of interest

None.

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