

Vogt-Koyanagi-Harada Syndrome Masquerading as Isolated Headache Despite a Reassuring Workup: A Case Report

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Abstract

Vogt-Koyanagi-Harada (VKH) syndrome is an autoimmune disease that can present with non-specific prodromal symptoms such as headache, and when the diagnosis is delayed, it can progress to legal blindness. We present a case of a 48-year-old female with type 2 diabetes, hyperlipidemia, and class II obesity who presented with progressive frontal headache radiating to the malar region, followed by bilateral ocular pain, blurred vision, and photopsia. Examination and imaging demonstrated bilateral multifocal exudative retinal detachments, choroidal folds, and disc edema with angiographic findings of active choroidal inflammation; infectious and autoimmune mimickers were excluded, and she met diagnostic criteria for acute VKH. High-dose corticosteroids produced only transient improvement, with recurrence on taper. Adalimumab achieved marked improvement, but coverage was subsequently discontinued for non-medical, insurance-related reasons, prompting transition to mycophenolate mofetil, which maintained clinical improvement through six months of follow-up. This case underscores that VKH, and systemic inflammatory disease more broadly, can hide behind isolated headache despite an entirely reassuring initial workup, and that a normal early evaluation should not close the diagnostic loop when visual symptoms are present. Secondarily, we describe an alternative regimen with second-line treatment with mycophenolate mofetil when biologic access is interrupted for non-medical reasons.

Categories: Other, Rheumatology, Ophthalmology

Keywords: adalimumab, chronic uveitis, exudative retinal detachment, mycophenolate acid mofetil, mycophenolate mofetil, steroid-sparing therapy, vogt-koyanagi-harada syndrome

Introduction

Isolated headache is among the most common presenting complaints in general practice, and in most cases, it reflects a benign, self-limited process. However, a normal initial evaluation does not exclude an evolving systemic inflammatory or autoimmune process, and a subset of conditions, including Vogt-Koyanagi-Harada (VKH) syndrome. This rare disease can present with headache as its only manifestation for days to weeks before diagnostic ocular or systemic findings emerge [1-3].

VKH is a rare, T-cell-mediated autoimmune disorder directed against melanocyte-containing tissues of the eyes, inner ear, meninges, skin, and hair; it disproportionately affects individuals of Asian, Hispanic, Middle Eastern, and Native American descent and is uncommon in lightly pigmented populations [4]. Ocular involvement classically manifests as bilateral granulomatous panuveitis with serous retinal detachments. Clinically, the disease progresses through four recognized stages, namely, prodromal, acute uveitic, convalescent, and chronic recurrent, which describe the course of the disease. Based on the revised international diagnostic criteria, categories are complete, incomplete, or probable disease, based on the involvement of bilateral ocular involvement plus both neurological/auditory findings and integumentary findings; bilateral ocular involvement plus either neurological/auditory findings or integumentary findings; and bilateral ocular involvement with acute features without neurological, auditory, or skin manifestations, respectively [5]. The prodromal stage often produces exactly the kind of nonspecific, isolated headache described above, sometimes accompanied by other easily overlooked symptoms, before the hallmark ocular findings appear and while initial infectious and autoimmune serologies remain unremarkable.

Once suspected and diagnosed, VKH also poses a therapeutic challenge that is less often discussed. Durable disease control typically requires early transition from corticosteroids to steroid-sparing immunomodulatory therapy (IMT); this approach is supported by the Fundamentals of Care for Uveitis (FOCUS) consensus recommendations and by comparative data showing similar efficacy between biologic and non-biologic IMT regimens in VKH [6,7]. Early IMT is strengthened in patients with pre-existing metabolic disease, in whom prolonged high-dose corticosteroid exposure carries material risk of worsening glycemic control, dyslipidemia, and weight gain. In practice, however, access to biologic agents such as adalimumab is frequently interrupted by insurance authorization barriers, which have been shown to delay initiation of IMT for uveitis by weeks and to impose substantial administrative burden on treating physicians [8]. Published guidance on preserving improvement of symptoms when a biologic must be discontinued for non-medical reasons is limited [9].

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We report a case of VKH syndrome in which a 48-year-old female with type 2 diabetes, hyperlipidemia, and class II obesity experienced several weeks of isolated headache and an entirely unremarkable initial infectious and autoimmune workup before ophthalmologic evaluation revealed bilateral exudative retinal detachments and active choroidal inflammation prompting further work-up. This case illustrates how VKH and systemic inflammatory disease can be masked by a reassuring early evaluation. Secondly, we describe a treatment pathway from corticosteroid-refractory disease to adalimumab-induced improvement, followed by an insurance-driven transition to mycophenolate mofetil, a first-line treatment for initial presentation rather than refractory disease, based on the First-Line Antimetabolites for Steroid-Sparing Treatment (FAST) Uveitis Trial [10]. The patient remained symptom-free at six months.

Case Presentation

A 48-year-old female with type 2 diabetes mellitus, hyperlipidemia, and class II obesity, with no prior ocular disease, presented with a three-week history of progressive headache. Symptoms began with malar pain that worsened with facial movement; three to four days later, this progressed to an intermittent frontal headache with only partial, transient relief from acetaminophen. Approximately one week after headache onset, she developed episodic blurred vision, prompting initial medical evaluation.

Laboratory workup at that time was negative for infectious, inflammatory, and autoimmune mimickers, including antinuclear antibody, antineutrophil cytoplasmic antibody, and syphilis serology; erythrocyte sedimentation rate and C-reactive protein were mildly elevated, and rheumatoid factor was minimally increased (Table 1). Brain imaging, including computed tomography, magnetic resonance imaging, and magnetic resonance angiography, showed no acute abnormalities. Given the progression to visual symptoms, she was referred to ophthalmology.

Laboratory parameter	Patient result	Reference range	Interpretation
Antinuclear antibody (ANA)	Negative	Negative (titer <1:40)	Negative
Antineutrophil cytoplasmic antibody (ANCA)	Negative	Negative	Negative
Syphilis serology (rapid plasma reagin/treponemal)	Non-reactive	Non-reactive	Negative
Erythrocyte sedimentation rate (ESR)	31 mm/h	0-20 mm/h	Mildly elevated
C-reactive protein (CRP)	3.10 mg/dL	<1.0 mg/dL	Mildly elevated
Rheumatoid factor (RF)	16 IU/mL	<14 IU/mL	Minimally increased

TABLE 1: Laboratory investigations obtained at initial evaluation.

At ophthalmologic evaluation, during the fourth week of illness, best-corrected visual acuity was hand motion in the right eye and 20/50 in the left eye. Intraocular pressure was 15 mmHg in the right eye and 17 mmHg in the left eye. Slit-lamp examination showed no anterior chamber cells or flare in either eye, with 2+ vitreous cells bilaterally. Dilated fundus examination demonstrated bilateral multifocal exudative retinal detachments, choroidal folds, and optic disc edema (Figures 1, 2). Fundus fluorescein angiography revealed multiple early pinpoint hyperfluorescent leaks with progressive late pooling corresponding to the areas of serous retinal detachment, as well as optic disc hyperfluorescence (Figures 3, 4), findings consistent with active choroidal inflammation. Given this evidence of retinal detachment, oral prednisone was initiated, and the patient was diagnosed with an acute complete VKH syndrome, due to bilateral eye involvement and headache with intermittent episodes of blurry vision as neurological symptoms, based on the revised international diagnostic criteria [5].

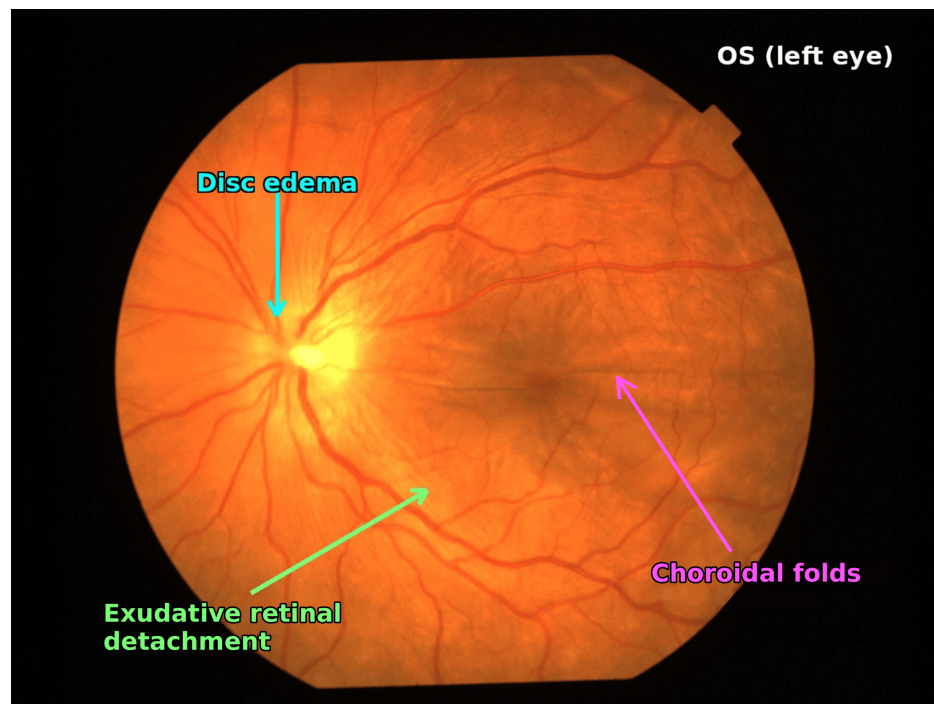


FIGURE 1: Multifocal exudative retinal detachment with choroidal folds and disc edema (OS).

Optic disc edema (blue arrow). The macula appears duller and darker than the surrounding retina, with loss of the foveal reflex and a mottled, irregular reflectivity extending inferotemporally. The overlying vessels show a subtle change in focus, suggestive of a shallow exudative retinal detachment (green arrow). A horizontal dark line temporal to the fovea represents a choroidal fold (magenta arrow).

OS: left eye.

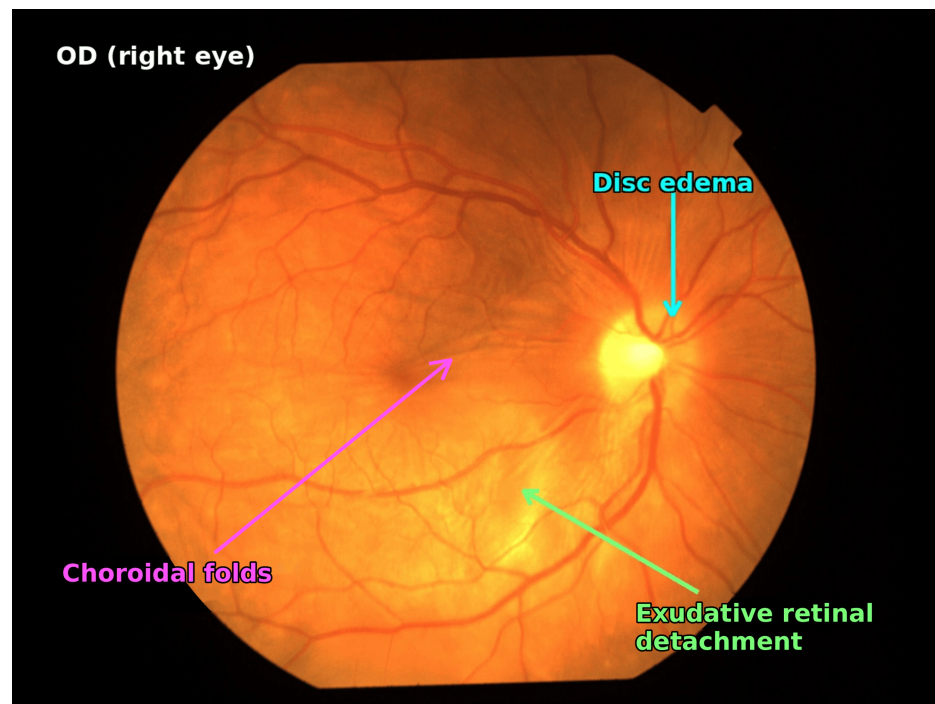


FIGURE 2: Multifocal exudative retinal detachment with choroidal folds and disc edema (OD).

Optic disc edema with blurred margins and peripapillary hyperemia (blue arrow). The posterior pole shows a dull, opaque, yellowish-gray appearance with loss of the normal choroidal vascular pattern and a blunted foveal reflex, consistent with subretinal fluid. Inferior to the disc and macula, there is a paler, placoid area of altered reflectivity over which the retinal vessels appear slightly out of focus, suggesting shallow serous elevation of the retina (green arrow). Horizontal linear striae between the disc and the fovea correspond to choroidal folds (magenta arrow).

OD: right eye.

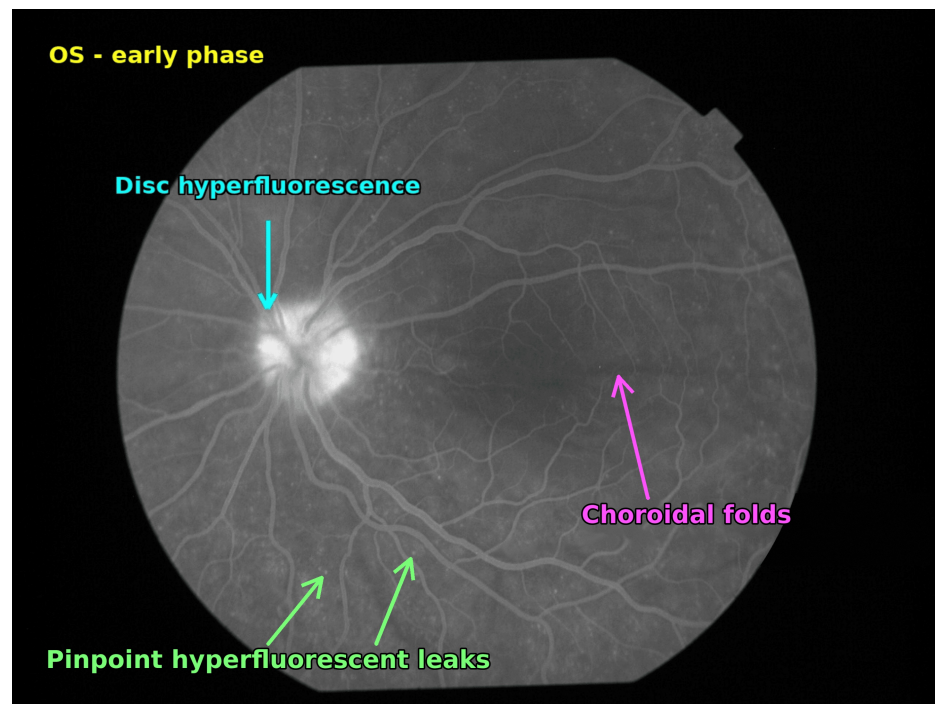


FIGURE 3: Areas of disc hyperfluorescence and pinpoint hyperfluorescent leaks suggesting active choroidal inflammation in the left eye (OS).

Disc hyperfluorescence (cyan arrow) and multiple pinpoint hyperfluorescent foci at the level of the retinal pigment epithelium in the posterior pole and inferior macula (green arrows). A hypofluorescent horizontal line temporal to the fovea corresponds to the choroidal fold seen clinically (magenta arrow).

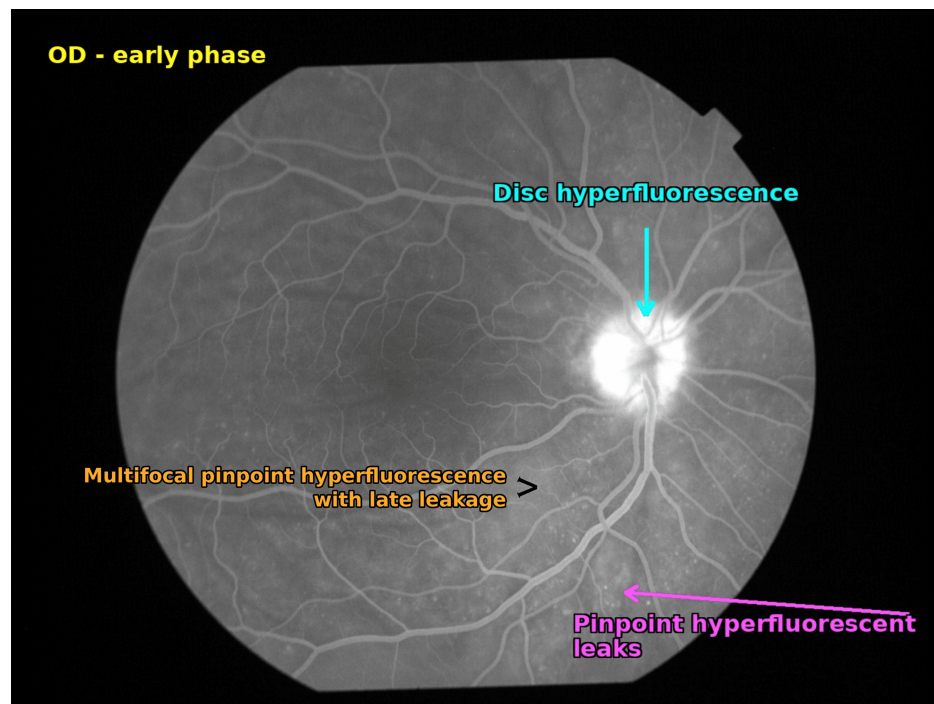


FIGURE 4: Areas of disc hyperfluorescence and pinpoint hyperfluorescence with late leaks suggesting active choroidal inflammation in the right eye (OD).

Disc hyperfluorescence (blue arrow) and multifocal pinpoint hyperfluorescence in the inferior posterior pole (arrowhead and magenta arrow), which progressed to late leakage with subretinal pooling, confirming active choroidal inflammation with serous retinal detachment.

Prednisone 40 mg/day for seven days, followed by a taper, produced transient improvement; however, symptoms recurred by the end of the first week of treatment during the taper of 30 mg/day, indicating steroid-dependent disease. Since the disease recurred after steroid tapering, it was considered recurrent; therefore, the next step was to initiate biologic therapy rather than early immunomodulatory therapy. Subsequently, prednisone was escalated to 70 mg/day (approximately 1 mg/kg/day), and adalimumab was introduced as steroid-sparing immunomodulatory therapy during the second week of steroid treatment, resulting in marked clinical improvement. Because continued biologic therapy was not approved by the patient's insurance, treatment was transitioned to mycophenolate mofetil 500 mg three times daily and prednisone with tapering dose weekly to minimal tolerated to 20 mg/day, which was well tolerated and maintained disease remission. At six-month follow-up, the patient remained asymptomatic and is being followed up closely with ocular imaging for evaluation of recurrent ocular inflammation.

Discussion

The main lesson of this case is diagnostic. Isolated, non-specific headache in this patient radiating to the periorbital and malar region can precede the ocular stage of VKH by days to weeks, often accompanied by an entirely reassuring infectious and autoimmune workup [1-3]. This pattern reflects the disease's prodromal stage, during which the same T-cell-mediated autoimmune response against melanocyte-associated antigens that will later produce granulomatous panuveitis is already active but has not yet produced findings detectable outside a dilated fundus examination [4,5]. Because initial laboratory testing at this stage is expected to be negative, clinicians evaluating a patient with persistent, otherwise unexplained headache, particularly when accompanied by even mild or intermittent visual symptoms such as photopsia, should resist the reassurance of a normal workup and maintain a low threshold for ophthalmologic referral. The mildly elevated rheumatoid factor in this patient illustrates a related pitfall: it can be misread as evidence for a rheumatoid-associated uveitis mimicker, but the revised diagnostic criteria for VKH remain primarily clinical and ophthalmic, and a low-titer rheumatoid factor elevation should not delay treatment or referral when other findings are otherwise classic [5]. Lumbar puncture, which can show a lymphocytic pleocytosis during the prodromal stage, was not performed in this case since the clinical and imaging findings were already sufficient for diagnosis; its omission is noted as a limitation rather than a diagnostic gap.

This case also has an important therapeutic dimension. Recurrence during corticosteroid taper indicates steroid-dependent disease, a recognized risk factor for progression to the chronic recurrent stage and worse

long-term visual outcomes if IMT is delayed [6,7,10,11]. Adalimumab, an anti-tumor necrosis factor biologic with demonstrated efficacy in non-infectious uveitis and specifically in VKH cohorts, produced marked improvement in this patient [10,12]. The rationale for prioritizing a steroid-sparing agent was reinforced by her metabolic profile: type 2 diabetes, hyperlipidemia, and class II obesity are all conditions that could be exacerbated by prolonged high-dose glucocorticoid therapy and would be expected to worsen, making early IMT a clinical priority rather than an optional escalation.

This case presents a clinically informative treatment sequence. Current management paradigms for VKH are corticosteroids as first-line. For early immunomodulatory therapy, mycophenolate mofetil and other conventional agents are considered adjunctive therapy to steroids. Biologics such as adalimumab are recommended for refractory disease despite initial therapy with steroids [6,7], as occurred in our patient, whose steroid-dependent recurrence during taper prompted escalation to adalimumab. Once symptom resolution is achieved, recommendations are to continue with biologics. However, adalimumab was discontinued not for a clinical reason but for an insurance-related one, representing a disruption to biologic access that is an increasingly recognized real-world challenge in the management of non-infectious uveitis, yet remains infrequently addressed in the VKH literature, which more often describes elective treatment sequencing than access-driven substitutions [8,9]. Notably, mycophenolate mofetil, though typically considered a first-line agent rather than a maintenance strategy after biologic induction, was sufficient in our case to preserve clinical improvement that adalimumab had achieved. This case describes how conventional immunosuppression may serve not only as initial therapy but also as a maintenance therapy when continued biologic access is not feasible, consistent with comparative data showing that non-biologic immunomodulatory therapy can achieve outcomes similar to biologic therapy in VKH [7]. These data are shown as educational since recommended therapy remains the gold standard therapy but was not available for our patient due to cost.

More broadly, VKH carries a substantial risk of progression to the chronic recurrent stage, with complications including sunset-glow fundus changes, secondary glaucoma, and subretinal fibrosis, particularly when initial corticosteroid therapy is inadequate, or IMT is delayed [4,10,11]. Comparative outcome data indicate that both biologic agents and conventional immunosuppressants, including mycophenolate mofetil, methotrexate, and calcineurin inhibitors, can achieve favorable long-term control when initiated early and matched appropriately to disease severity [7,12]. Our patient's course showed that biologic therapy successfully improved clinical symptoms, but alternative treatment was required to maintain disease control.

This case report has several limitations. As a single-patient report, its findings cannot be generalized. A six-month follow-up is relatively short, given the known risk of late recurrence in VKH. Human leukocyte antigen (HLA) typing and cerebrospinal fluid analysis were not performed, although either could have further supported the diagnosis. In addition, remission has not yet been confirmed with multimodal imaging (indocyanine green angiography (ICGA), optical coherence tomography angiography (OCTA), enhanced depth imaging optical coherence tomography (EDI-OCT), and fundus fluorescein angiography (FFA)). As VKH was diagnosed clinically, treatment decisions were guided mainly by the patient's symptomatic improvement. Follow-up ocular imaging is planned for upcoming visits to document remission objectively.

Conclusions

This case highlights that a severe systemic inflammatory disease may present as an intermittent headache despite a reassuring initial laboratory and radiographic evaluation. The normal early workup reflects the limits of the tests performed and that a dedicated history is key in identifying features such as a headache poorly responsive to analgesia and subtle visual symptoms such as blurred vision that should prompt further workup. Early referral prevented vision-threatening complications. Secondly, when adalimumab was discontinued for non-medical reasons, transition to mycophenolate mofetil maintained symptom-free status over six months of follow-up. Although this observation derives from a single patient and cannot establish equivalence, it suggests that a conventional immunosuppressive agent may be a reasonable option when biologic access is interrupted, particularly in patients with metabolic comorbidities in whom renewed high-dose corticosteroid exposure is undesirable.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Critical review of the manuscript for important intellectual content: Alejandra P. Rivera Caro, Jose Ibanez-Moran, Milton D. Carrero Quiñones, Josean M. Rosado Rivera

Disclosures

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