• Letter to the Editor •

Late onset acute Vogt-Koyanagi-Harada syndrome-challenges on the way

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Dear Editor,

We would like to share some clinical cases of late onset acute Vogt-Koyanagi-Harada syndrome (VKH), a rare diagnosis in this age range.

This is an autoimmune inflammatory condition mediated by T cells that target melanocytes, manifests as a severe bilateral granulomatous panuveitis and is associated with systemic involvement, including central nervous system, audiovestibular and dermatological findings[1]. It usually affects women in their second to fourth decade of life, and is more common in Asia, Latin America and Middle East[1]. However, newer cases among elderly seem to be growing, as recently reported, with 10% of a Japanese cohort of VKH patients being diagnosed after 65y[2]. Adding to this, there were other reports in the literature regarding older patients, with the oldest patient diagnosed at 89y, in Asia[3].

Clinical features, proposed treatment, side effects and management of three patients with late onset acute disease are described. The diagnosis was based on the Revised Diagnosis Criteria for VKH-2001[4].

Case 1 A 62y Caucasian man presented with painless, rapidly progressive visual loss in both eyes (OU) for 2wk, and ocular hyperemia, holocranial headache, tinnitus and hearing loss. No history of ocular trauma or surgery was reported.

Best corrected visual acuity (BCVA) was light perception (LP) OU. Slit-lamp examination (SLE) demonstrated: conjunctival hyperemia, cornea with Descemet's folds, fine keratic precipitates (KP), shallow anterior chamber and Tyndall 3+ OU. Fundoscopy showed vitritis 1+, hyperemic edematous optic disc with total serous retinal detachment (RD) OU. Ocular ultrasonography showed total exudative RD and choroidal detachment 360° OU (Figure 1). Infectious and autoimmune causes were excluded.

Pulse therapy with methylprednisolone 1 g/d for 3d was initiated and hallucinations developed. Treatment then followed to oral prednisone 1 mg/kg·d with prednisolone acetate 1% and tropicamide 1% drops. Two weeks later, despite ocular and systemic improvement, BCVA was still LP OU. By this time, the patient experienced dizziness, weight gain and systemic arterial hypertension (SAH). Intravitreal injections of triamcinolone acetonide (IVT) OU was given along with oral cyclosporine 5 mg/kg·d, and slow tapering of oral steroids was initiated.

During follow-up, he developed 2 episodes of anterior segment recurrences and posterior subcapsular cataracts (PSC). Alopecia, poliosis and hair depigmentation were also observed. After 15mo follow-up, he was still on cyclosporine 5 mg/kg·d and prednisone 10 mg/d. BCVA improved to 20/70 in OD and 20/40 in OS.

Case 2 A 62y Caucasian male presented with painless and sudden visual loss OU for 4d. BCVA in OD was 20/70 and 20/200 in OS. There was no prior history of surgical or ocular trauma.

He had granulomatous KPs and Tyndall 2+ OU on SLE and fundoscopy showed serous RD OU and hyperpigmentation areas in mid periphery of OD (Figure 2). Infectious and autoimmune testing was negative.

Oral prednisone 1.5 mg/kg·d and topical treatment OU were started and after 1mo, BCVA improved to 20/40 OU. However, cystoid macular edema OU was present and IVT OU was performed after which slow tapering of oral and topical steroids was attempted. Nevertheless, the patient had two recurrences manifesting as new RD OU, responsive to high dose oral and IVT. Cataracts OU developed and systemic side

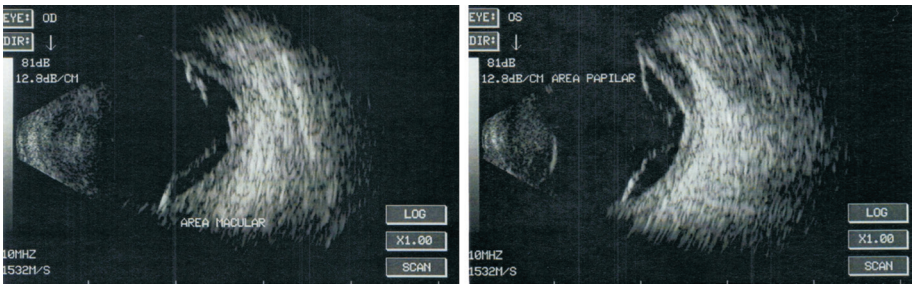

Figure 1 Ocular ultrasonography Total serous retinal detachment. No retinal tears and 360° choroidal detachment OU.

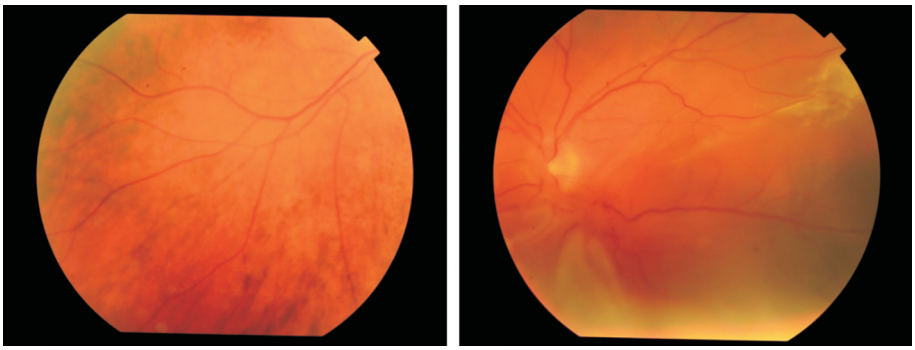

Figure 2 Retinography before treatment OD showing areas of retinal hyperpigmentation in the mid periphery and OS showing serous retinal detachment, respectively.

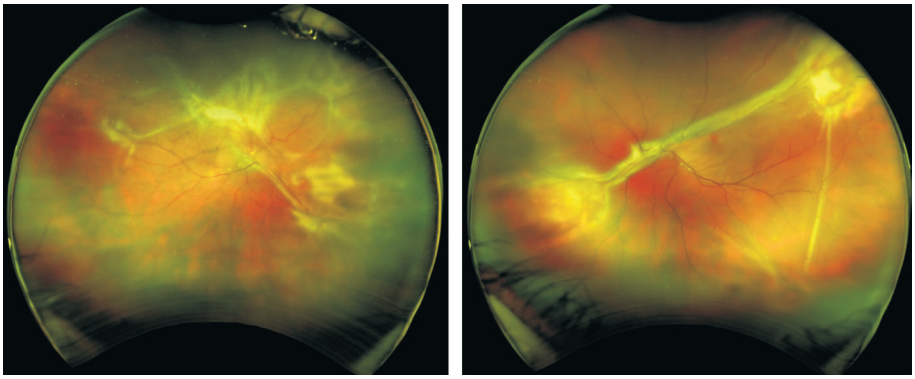

Figure 3 Retinography before surgery Total serous detachment in OU with advanced PVR in OD and OS, respectively.

effects included SAH, hyperglycemia and weight gain. Oral cyclosporine 5 mg/kg·d was introduced so oral steroids could be slowly tapered to 12.5 mg/d. Final BCVA was 20/40 OU.

Case 3 A 70y Caucasian woman with episodes of fever and malaise for 3mo, followed by visual loss 1mo before, came to our department. She was already on oral prednisone 40 mg/d. Past medical history included systemic arterial hypertension and ophthalmological background was unremarkable.

At examination BCVA was hand movements in OD and LP in OS. Brownish KPs, posterior synechiae and PSC OU were present. Fundoscopy showed total serous RD with extensive areas of proliferative vitreoretinopathy (PVR) OU (Figure 3).

Systemic steroids dosing was maintained and additional local treatment was given: IVT in OD and dexamethasone intravitreal implant in OS. Despite initial improvement in OS, one month later BCVA dropped to LP OU associated with bilateral serous RD. Pulse therapy was initiated but SAH became uncontrolled and she needed to be admitted to the hospital.

During the following 4mo, despite oral cyclosporine 8 mg/kg·d, azathioprine 3.5 mg/kg·d and steroids 0.75 mg/kg·d, systemic symptoms disease-related totally improved, ophthalmological examination remained unchanged and SAH was still difficult to control. Phacoemulsification with intraocular lens implantation, posterior vitrectomy with membrane peeling, endolaser and silicone oil tamponade was performed OU. However, VA remained unchanged.

The authors believe these cases represent a good opportunity to emphasize the trend on the diagnosis of VKH in more advanced ages. These cases may not only have unusual demographical characteristics (since all patients were Caucasian Brazilian, two of whom were men) but also a more aggressive course and hard to control disease. Clinical evaluation, treatment and outcomes are summarized in Table 1.

Older patients pose several challenges. The diagnosis may be delayed and difficult to establish, compromising outcomes: systemic and ocular comorbidities (cataract and macular

Table 1 Demographics, clinical characteristics and outcomes

Clinical Presentation, Management and Outcome	Case 1	Case 2	Case 3
Sex	Male	Male	Female
Age (y)	62	62	70
Ethnicity	Caucasian	Caucasian	Caucasian
Ocular manifestations	Severe anterior segment signs: Tyndall 3+; severe posterior segment signs: hyperemic optic disc, choroidal detachment (besides serous RD)	Severe anterior segment signs: mutton-fat KP; Tyndall 2+; serous RD	Severe anterior segment signs: mutton-fat KP; posterior synechiae; serous RD with PVR
Systemic manifestations	Headache, tinnitus, hearing loss	Painless and sudden visual loss	Fever, malaise
Time elapsed until treatment	2wk	4d	Over 1mo
Systemic steroid treatment	Pulse therapy; prednisone 1 mg/kg·d	1.5 mg/kg·d	0.75 mg/kg·d and pulse therapy
Local adjuvant therapy	OD: IVT; OS: IVT	None	OD: IVT; OS: dexamethasone implant
IMT	Cyclosporin 5 mg/kg·d	Cyclosporin 5 mg/kg·d	Cyclosporin 8 mg/kg·d; azathioprine 3.5 mg/kg·d
Side effects	Hallucinations, dizziness, SAH, weight gain	SAH, hyperglycemia, weight gain	Uncontrolled SAH
Follow-up	2 episodes of anterior segment recurrences; alopecia, poliosis, vitiligo	2 episodes of posterior segment recurrences	No improvement
Initial BCVA	OD: LP; OS: LP	OD: 20/70; OS: 20/200	OD: HM; OS: LP
Final BCVA	OD: 20/70; OS: 20/40	OD: 20/40; OS: 20/40	OD: HM; OS: LP

HM: Hand movements; IVT: Intravitreal triamcinolone; KP: Keratic precipitates; LP: Light perception; OD: Right eye; OS: Left eye; PVR: Proliferative vitreoretinopathy; RD: Retinal detachment; SAH: Systemic arterial hypertension.

disease) may mimic VKH's signs and elderly patients may find more difficult to access health care system[3]. Fortunately, the first two cases were diagnosed within a month after initial symptoms. However, that was not the case with patient 3, with longer time elapsed until diagnosis, which could have contributed to the outcome.

Once the diagnosis is established, clinical manifestations of VKH seem to be more aggressive in elderly. The largest cohort with patients older than 60y included 7 cases, in which cataract, optic disc hyperemia and choroidal detachment were more likely to occur, possibly correlating with more severe inflammation. Adding to this, elderly patients needed higher steroids dose than younger, supporting this hypothesis[2]. Our cases corroborate these and add further information: all patients presented severe anterior and posterior segment manifestations (such as hyperemic optic disc, serous RD with or without PVR, choroidal detachment), all had systemic involvement and all developed cataract (in which both inflammatory trigger and IVT injections might have contributed). Moreover, cases 1 and 2 presented recurrences during steroid tapering and while on immunosuppressants, and case 3 did not improve, demonstrating the severity and persistency of inflammation.

Treatment is the third challenge. The majority of these patients have comorbidities and adequate disease control without compromising general health is difficult[3]. Standard treatment includes early high dose systemic steroids (≥1 mg/kg), preferably within 2wk from the beginning of symptoms, followed by slow tapering. Treatment should be no less than 6mo and the dose should not be below 0.75 mg/kg·d until 4th month, titrated according to inflammation's level[5-6]. All our patients had high dose steroid therapy although adequate time and dose was impossible due to side effects: overall our patients developed weight gain, hallucinations, dizziness, hyperglycemia and uncontrolled high blood pressure, forcing earlier tapering.

Local steroids and systemic immunosuppressive therapy (IMT), may be used in association with systemic steroids to reduce their dose or even precluding their use in selected cases, while promoting adequate control of inflammation. Almost 78% of VKH patients treated with isolated posterior subtenon triamcinolone in acute onset VKH had complete resolution of ocular disease[7]. Fluocinolone acetonide implant may also reduce daily oral steroid dose and recurrence rates[8]. In our report, all eyes were treated with intravitreal steroids. Increase in local suppression of inflammation occurred in cases 1 and 2, but not in the long run in case 3, possibly due to its impressive severity. Regarding IMT, there is still no consensus regarding which agent is more advantageous and which patients would benefit the most. A significant reduction in recurrence rates, late complications and improvement in visual outcome in acute disease was reported with IMT combined with steroids as first-line therapy[9]. However, Urzua *et al*[10] emphasized that earlier IMT in association with steroids was only superior in patients with initial visual acuity ≤20/200, fundus depigmentation, chronic disease and tinnitus. Regarding agent choice, there are

no randomized controlled clinical trials to support one specific agent. Cyclosporine performed better as a steroid-sparing agent in a study with chronic VKH patients[11] but methotrexate and mycophenolate mofetil achieved good results in another study involving acute and chronic VKH patients[12]. Our patients received early cyclosporine due to the severe initial presentation and although infections were a concern, no events were reported.

Although visual prognosis is good in the majority of cases, with 70%-80% with BCVA≥20/40[13], more than half may progress to chronic disease, due to delayed treatment and suboptimal dosing, or develop complications (cataract, glaucoma, choroidal neovascularization and subretinal fibrosis)[5,14]. Clinical presentation, such as poor VA (≤20/200), severe anterior segment inflammation (mutton-fat KPs, anterior chamber reaction ≥2+, iris nodules and posterior synechiae) and less exudative RD may be associated with chronic recurrent disease[13]. However, adequate steroid therapy remains the most important factor influencing outcome[14]. In our series, despite early treatment in cases 1 and 2, 5/6 eyes presented final VA≤20/40 and major contributors to these results were probably the severity of initial presentation and the need of early steroid tapering.

Some authors theorize that posterior recurrences and those occurring within six months are usually associated with failure regarding steroid treatment (late initiation, inadequate dose and quick or early withdrawal) leaving some specific T-cells against active melanocytes that cause subsequent recurrences[15]. This was the case with patients 1 and 2, emphasizing the difficulty in managing these patients and the concomitant higher level of inflammation[2].

In conclusion, although not common, VKH may occur in patients above 60y. In this setting, inflammation can be more severe and hard to control. High-dose steroid therapy should be started as soon as possible, but side effects may preclude it, especially in this subset of patients in which systemic comorbidities are common. Considering this, other therapeutic options, such as local steroids injections and IMT, should be considered early in the course of disease.

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