Sympathetic ophthalmia or Vogt-Koyanagi-Harada disease: Don't judge a book by its cover

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Abstract:

A 17-year-old female patient of Asian origin presented to the Ocular Immunology Unit of Reggio Emilia Hospital in July 2017, complaining of nausea, vomiting, low-grade fever, tinnitus, and headache going on for 3 days, followed by the appearance of blurred vision in the left eye. Three months before (April 2017) she had a history of penetrating keratoplasty in the right eye for a diagnosis of Acanthamoeba keratitis unresponsive to antiamoebic therapy. The clinical examination exhibited a picture of bilateral panuveitis with papillitis and exudative detachment of the retinal neuroepithelium. The diagnostic workup excluded a possible infectious etiology and showed the positivity of the human leukocyte antigen-DR4. Magnetic resonance imaging showed leptomeningeal inflammatory involvement and lumbar puncture revealed lymphocytic pleocytosis. Considering the history of trauma, Vogt-Koyanagi-Harada disease was ruled out and the diagnosis of sympathetic ophthalmia was made. The patient was treated with topical and oral steroids combined with mycophenolate mofetil for long-term control of the disease. The subsequent 18-month follow-up showed an excellent clinical response with a marked improvement in the ocular findings.

Keywords:

Panuveitis, penetrating keratoplasty, sympathetic ophthalmia, Vogt-Koyanagi-Harada disease

Introduction

Sympathetic ophthalmia (SO) is a rare, bilateral granulomatous panuveitis occurring after ocular trauma or surgery. Different conditions can mimic the ophthalmic manifestations of SO disease, including Vogt-Koyanagi-Harada (VKH) disease.

A 17-year-old patient presented to our clinic with bilateral granulomatous panuveitis. 3 months before she had undergone a penetrating keratoplasty (PK) for Acanthamoeba keratitis unresponsive to topical treatment in the right eye (RE). A provisional diagnosis of VKH was possible. However, the history of PK allowed us to confirm the diagnosis of SO. This uncommon case report is presented to emphasize the difficulties in establishing a differential diagnosis between SO and VKH disease, especially in the early phase of these conditions.

Case Report

A 17-year-old Asian female patient had a history of PK in the RE, performed in April 2017 for an Acanthamoeba keratitis unresponsive to topical drugs. After 3 months (July 2017), she was referred to our clinic, the Ocular Immunology Unit of Reggio Emilia Hospital, because of a suspected uveitis. According to the patient, 3 days before, she developed nausea, vomiting, low-grade fever, tinnitus, and headache, followed by the onset of blurred vision in the left eye (LE). She denied any systemic illness. On examination, her visual acuity (VA) was hand motion in the RE and counting fingers in the LE. A slit-lamp examination showed circumciliary congestion in both eyes. The RE presented an opacity covering the whole transplanted cornea with vascularization of the recipient bed. The anterior chamber was shallow with total cataract and seclusio pupillae. The LE had granulomatous keratic precipitates of medium size, the anterior chamber was deep with a 3 mm hypopyon and posterior synechiae were present [Figure 1].

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Intraocular pressure was normal in both eyes. Fundus examination was not possible due to the opacity of the cornea in the RE, the intense inflammation in the anterior chamber of the LE and poor patient cooperation. Optical coherence tomography (OCT), fundus fluorescein, and indocyanine green angiography were not performed as well. Thus, an ocular ultrasound was done: both eyes shared similar findings, that is, a diffuse low-to-medium-reflective thickening of the posterior choroid, most prominent in the peripapillary area, multiple areas of exudative retinal detachment (RD), and vitreous opacities with no posterior vitreous detachment [Figure 2]. A complete workup for uveitis was requested. The full blood count test was normal. Liver and renal function tests, double-stranded DNA and antinuclear antibody, erythrocyte sedimentation rate, angiotensin-converting enzyme, and lysozyme were normal. Infections were ruled out as well: serum herpesvirus, serum toxoplasmosis, serum Bartonella, serum Borrelia, QuantiFERON-TB Gold test, screening tests for syphilis, and HIV tests were negative. An anterior chamber tap was requested, which led to the detection of CD20 lymphocytes in the aqueous humor. The human leukocyte antigen (HLA)-DR4 was positive. Brain magnetic resonance imaging showed a diffuse leptomeningeal inflammatory involvement consistent with meningism [Figure 3]. Consequently, a lumbar puncture was performed, revealing lymphocytic pleocytosis in the cerebrospinal fluid (387 lymphocytes/μl). The diagnosis of SO disease was made. Treatment was started with a daily bolus of methylprednisolone for 3 days in a row (1 g per day), followed by oral steroids (1 mg/kg per day) combined with mycophenolate mofetil (2 g per day) for long-term control of the disease. Topical steroids and cycloplegic eyedrops were also prescribed in both eyes, and oral prednisolone was tapered by 5 mg every 2 weeks. By the 2nd week of therapeutic follow-up, it was possible to examine the fundus and to perform an OCT scan in the LE. The imaging showed choroidal thickening with hyper-reflective dots, the presence of fluid under the retinal neuroepithelium, and the appearance of membranous structures continuous with the ellipsoid zone (inner segment (IS) and outer segment (OS)-junction of the photoreceptors), essentially made of fibrin and photoreceptors' disrupted OS. These findings completely disappeared in 6 months (January 2018), when VA was fully restored. These findings disappeared in 6 months (January 2018), with residual extrafoveal IS/ OS junction damage [Figure 4], accompanied by a good visual acuity. Moreover, ultrasound examination of the fellow eye (RE) also reverted to normal after 6 months [Figure 5], but VA did not improve both because of the corneal opacity and the cataract. After 1 year of follow-up, a second PK, combined with an extracapsular cataract extraction, was performed in the RE, with a good anatomical outcome. When compared to the LE, the RE's OCT scan revealed a better result, confirming the diagnosis of SO [Figure 6].

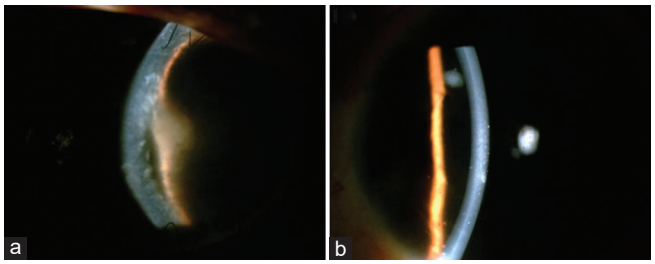

Figure 1: Slit-lamp examination of the right eye (a) showed an opacity covering the whole transplanted cornea. The anterior chamber was shallow with total cataract and seclusio pupillae. The left eye (b) had medium-sized granulomatous keratic precipitates

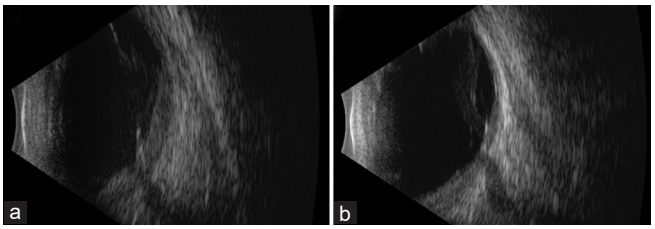

Figure 2: B-scan ocular ultrasound of the right eye (a) and the left eye (b) shared similar findings: A diffuse low-to-medium-reflective thickening of the posterior choroid, most prominent in the peripapillary area, multiple areas of exudative retinal detachment, and vitreous opacities

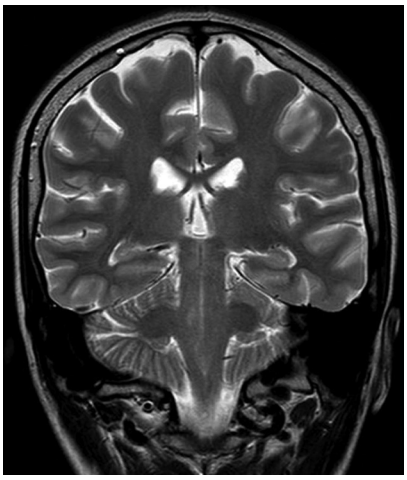

Figure 3: Brain magnetic resonance imaging shows a diffuse leptomeningeal inflammatory involvement

Discussion

SO constitutes a rare cause of bilateral granulomatous panuveitis, more frequently occurring after penetrating injuries.[1] The wounded eye is referred to as the "exciting" one, whereas the fellow eye as the "sympathizing" one. SO develops after a latent period following the trauma. About 70%–80% of the cases occur within 3 months of injury, whereas 90% within 1 year. The onset of SO is variable, ranging from 1 week to 66 years after the inciting trauma.[2]

SO might as well occur as a consequence of surgery, especially vitrectomy, which accounts for 1 in 800 cases. In addition, it is described after glaucoma, cataract, corneal transplant,[3,4] paracentesis, iridectomy, evisceration, and scleral buckle surgeries. Sporadic cases have also been documented following

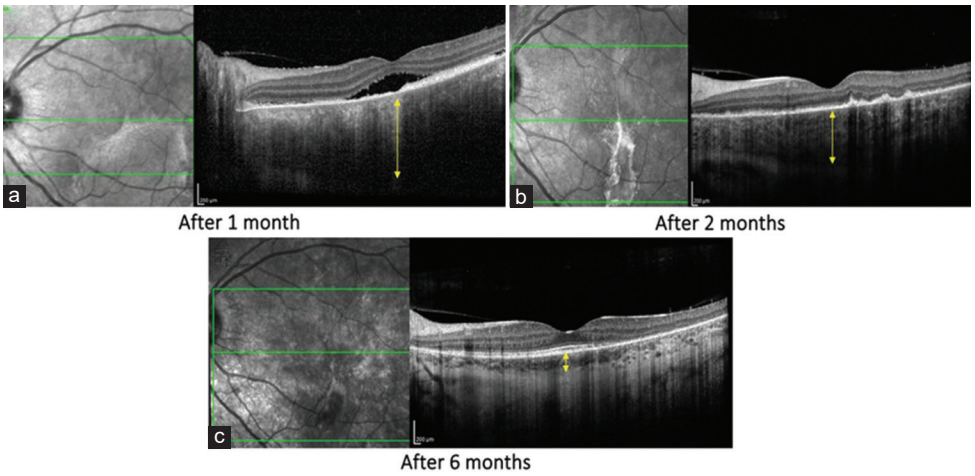

Figure 4: Left eye optical coherence tomography scan during therapeutic follow-up. After 1 month (a), choroidal thickening (arrow), hyperreflective dots, subfoveal fluid, and hyperreflective material inferiorly to the macula. These improved in 2 months (b) and disappeared in 6 months (c), with full visual acuity restoration

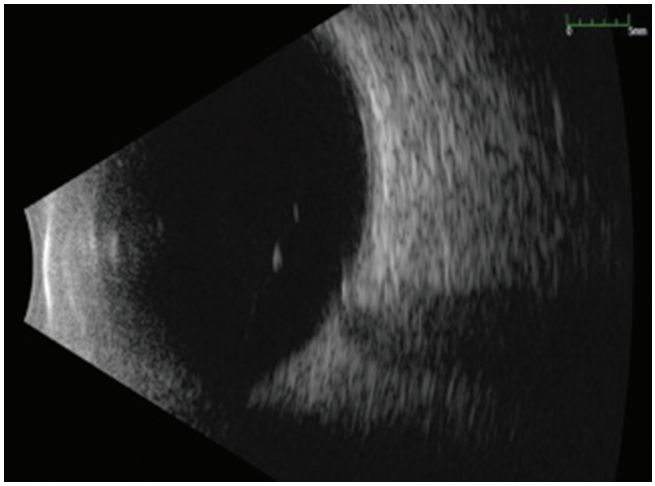

Figure 5: B-scan ocular ultrasound of the right eye after 6 months, compared to the first presentation [Figure 2a], showed the disappearance of the posterior choroidal thickening and of the areas of exudative retinal detachment

nonpenetrating conditions (fungal and Acanthamoeba keratitis,[5,6] irradiation for melanoma – brachytherapy plaque and proton therapy – laser procedures and cyclodestruction for neovascular glaucoma).

Ours is the first case of hypopyon in SO. This clinical sign, typical of HLA B27-related and Behçet's uveitis, has not yet been observed in the considered disease. Rathinam and Rao described a few cases of hypopyon in patients developing SO in eyes with postoperative bacterial endophthalmitis.[7] In these circumstances, the hypopyon was to be ascribed to the infectious condition, and had nothing to do with the subsequent diagnosis of SO.

Furthermore, to our knowledge, this is the first case of SO in which CD20 lymphocytes have been detected in the aqueous humor. In fact, so far, several authors have described the presence of CD20 lymphocytes in SO, but as the main constituents of choroidal infiltrates.[8-10] This finding is significant since it highlights a novel aspect of the disease. Basically, the discovery of these cells in the aqueous humor represents a new and previously unreported dimension of their involvement in such pathology. This finding may have implications for our understanding of the pathophysiology of SO and could potentially lead to new insights into its diagnosis and treatment.

The differential diagnosis of SO includes conditions such as VKH disease, sarcoidosis, syphilis, tuberculosis, and intraocular lymphoma. In our patient, test results for the last four conditions were negative. Consequently, the main differential diagnosis was with VKH disease.

Initially described as an uveomeningoencephalitic syndrome, VKH disease is a systemic granulomatous autoimmune disease that targets melanocyte-rich tissues.

Currently, the diagnosis of early-stage VKH is based on the criteria published by the Standardization of Uveitis Nomenclature (SUN) Working Group in 2021. These include:

1. Evidence of Harada disease: A. Serous (exudative) RD AND (b. and/or c.) b. Multiloculated appearance on fluorescein angiogram OR c. Septae on OCT

OR

2. Panuveitis with ≥2 of the following neurologic symptoms or signs: Headache OR tinnitus OR dysacusis OR meningismus OR cerebrospinal fluid pleocytosis

AND

3. No history of penetrating ocular trauma or vitreoretinal surgery before disease onset.

Diagnosis requires 1) or 2) AND 3).[11]

In 2021, the SUN Working Group also defined the classification criteria for SO:

1. History of unilateral ocular trauma or surgery

AND

2. Ocular inflammation, either bilateral OR if there is no

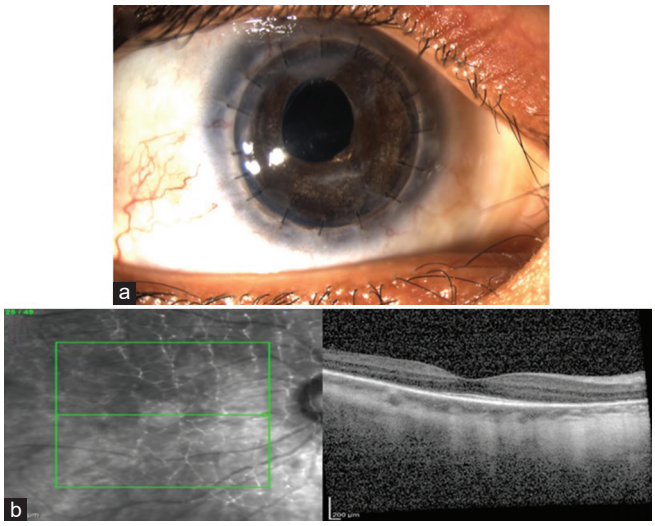

Figure 6: After 1 year of follow-up a second penetrating keratoplasty, combined with an extracapsular cataract extraction, was performed in the right eye (RE) (a), the RE's optical coherence tomography scan revealed a better result than the left eye's (b)

view in the inciting eye (e. g. enucleated, phthisis, and opaque cornea), then detectable inflammation in the sympathizing eye

AND

3. Evidence of more than isolated anterior uveitis, either anterior chamber and vitreous inflammation OR panuveitis with choroidal involvement.[12]

Our case describes a diagnostic dilemma where multiple factors are at play, making it challenging to definitively diagnose either SO or VKH disease. Analyzing the various elements:

1. Both SO and VKH disease are autoimmune disorders that target melanin-bearing cells.[13] They are almost identical in terms of histopathology and HLA-DR4, DRw53, and Bw54 predisposition. Therefore, these antigens cannot be used for a differential diagnosis between the two pathologies
2. History of PK: The patient's history is a strong indicator favoring SO as a potential diagnosis. A history of penetrating trauma is basically always present in SO, whereas its absence is a necessary condition to discuss VKH disease
3. Demographic factors: The patient being female and of Asian origin is more characteristic of VKH disease. SO does not show any sexual or racial predilection. In contrast, VKH disease is more common in females and due to greater skin pigmentation, in Asians.
   However, it is important to bear in mind that both SO and VKH disease can affect individuals of various backgrounds, so demographic considerations should be taken into account alongside other clinical findings.
4. Symptoms specific to VKH disease: The patient's symptoms closely resembling those of the prodromic phase of VKH disease are a noteworthy aspect. Systemic involvement, including skin changes, central nervous system (CNS) findings, and hearing dysfunction, is possible in SO, although it is greater and more typical of VKH disease.[14]
5. Lymphocytic pleocytosis: Kitaichi *et al*. found that about 80% of VKH disease patients had cerebrospinal fluid pleocytosis, mostly consisting of lymphocytes. This pleocytosis usually resolves within 8 weeks.[15] Pleocytosis is also described as possible in SO,[16,17] although systemic involvement is considered uncommon.

In our patient, the lumbar puncture revealed lymphocytic pleocytosis in the cerebrospinal fluid. Although not particularly specific, the presence of lymphocytic pleocytosis in the cerebrospinal fluid is an important finding. While it can be observed in both SO and VKH disease, it suggests inflammation within the CNS, which may be a sign of a number of inflammatory or autoimmune diseases.

In conclusion, in this complex clinical case, the history of PK performed 3 months before the development of uveitis was in favor of the diagnosis of SO. The similarities between VKH disease and SO highlight how difficult it is to differentiate between these two disorders, particularly in the early acute bilateral uveitic phase, and that the only element that allows one to discern these conditions is the history of trauma or surgery in SO.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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