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CASE REPORT

Vision-threatening bilateral panuveitis and TRAPS in a child: an uncommon association

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Abstract
Purpose To report a childhood case of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) carrying the R92Q variant with a vision-threatening bilateral panuveitis.
Methods Case report and review of the literature.
Results A 7-year-old boy presented with an active bilateral panuveitis and a macular rash associated with fever. Fundus examination showed two choroidal lesions on the posterior pole of the right eye, and fluorescein angiography revealed early hypofluorescence and late hyperfluorescence of the lesions, which were hyper-autofluorescent. Extensive clinical laboratory analyses ruled out autoimmune diseases and systemic infection. The only remarkable finding was a positive IgG for herpes simplex 1. He underwent two successive diagnostic pars plana vitrectomies as well as cataract and glaucoma surgeries. Genetic analysis revealed a mutation in the TNFRSF1A gene, and the patient was diagnosed with TRAPS-associated bilateral panuveitis. He was treated with adalimumab and has been free of active inflammation since then.
Conclusions We present here the first case reported of panuveitis in a patient with TRAPS. This finding stresses the increasing importance of genetic analysis in search of autoinflammatory diseases to establish an adequate diagnosis and treatment in cases of uveitis of unknown etiology.

Keywords Panuveitis · Autoinflammatory diseases · Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) · Maculopapular exanthema

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Introduction

Autoinflammatory diseases are an expanding group of conditions characterized by inflammation in the absence of autoantibodies or antigen-specific T cells [1, 2]. For these diseases, the components of the innate immune system are responsible for clinical manifestations. Among them, tumor necrosis factor receptor-associated periodic syndrome (TRAPS; OMIM #142680) is caused by mutations in the TNFRSF1A gene (OMIM #191190) [3, 4]. It is characterized by recurring inflammatory attacks, fever, abdominal pain, arthritis, and cutaneous manifestations [5]. Ocular involvement is common and includes conjunctivitis and periorbital edema, but intraocular inflammation has not been reported to date.

Here, we present the first reported case of severe bilateral panuveitis in the context of TRAPS in a 7-year-old boy carrying the R92Q variant.

Materials and methods

The patient was a 7-year-old child of healthy parents, without a family history of important diseases. Informed consent for the publication of this case has been obtained from the patient's parents. He was referred to the Ocular Immunology Unit of the Institute of Applied Ophthalmobiology (IOBA) for bilateral anterior uveitis with choroidal lesions in the right eye. He was healthy until 6 months before, when he developed a bilateral acute conjunctivitis. This was followed in a few days by fever and a maculopapular exanthema, beginning in the ears and perioral area and rapidly spreading to upper and lower extremities. Pathology analysis disclosed an erythema multiforme, with positive herpes simplex virus 1 IgG. His symptoms improved with oral acyclovir, but recurred after 5 months, accompanied then, with a bilateral acute anterior uveitis.

Examination at our clinic revealed a best-corrected visual acuity (BCVA) of 20/25 for the right eye (OD), 20/20 for the left eye (OS), 2 plus anterior chamber cells in both eyes (OU) [6], posterior synechiae OD, and normal intraocular pressure OU. Dilated fundus examination showed two choroidal yellow creamy lesions, nasal and inferior to the optic disk OD, vitreous cells, and 2 plus vitreous haze as viewed through binocular indirect ophthalmoscope (BIO-score) OU [6]. Fluorescein angiography (FA) showed early hypofluorescence and late hyperfluorescence, with widespread peripheral capillary leakage. There was also fundus autofluorescence (FAF), and the two lesions were hyper-autofluorescent (Fig. 1).

Clinical laboratory analyses were all normal for acute-phase reactants, angiotensin-converting enzyme (ACE), lysozyme, purified protein derivative (PPD), chest X-ray, autoantibodies, and infectious serologies. The only remarkable finding was the previously noted positive IgG for herpes simplex 1.

A diagnostic pars plana vitrectomy (PPV) was performed OD, and samples were sent to microbiology for culture, polymerase chain reaction (PCR), and pathology, all without any positive results. The patient was then treated empirically with oral famciclovir.

On follow-up examination at 1 year, we found new lesions in the posterior pole of both eyes. We performed a new PPV OD, along with cataract and glaucoma surgery OD. The PPV provided no new information. The patient was started on oral steroids and azathioprine, which partially stabilized the clinical picture.

Searching for an autoinflammatory etiology, we performed a genetic analysis that revealed the mutation R92Q in TNFRSF1A gene. Finally, the patient was diagnosed with TRAPS-associated bilateral panuveitis. He was started on adalimumab every other week, and this maintained control of the inflammation over a follow-up period of 16 months. During that time, the existing lesions appeared to be inactive, and no new ones developed (Fig. 2).

Results and discussion

The recurrent fever syndromes manifest as episodic inflammation without autoantibodies or antigen-specific T cells and conform an expanding group of diseases that may lead to heterogeneous ocular manifestations [7, 8]. These disorders usually originate with an exaggerated activation of the inflammatory process due to endogenous or exogenous factors, mediated by the inflammasome that triggers maturation of proinflammatory cytokines such as interleukin-1β and tumor necrosis factor α [9].

TRAPS is a dominantly inherited, multisystem inflammatory disorder, caused by a heterozygous mutation. The phenotype and clinical severity are highly variable [10]. Characteristic features include recurrent fever, abdominal pain, cutaneous and synovial inflammation, conjunctivitis, and periorbital edema, which typically last several days to weeks [1, 2]. A proportion of patients develop systemic amyloidosis, which is potentially life-threatening [11].

Ocular involvement is common in the autoinflammatory diseases. Among them, granulomatous disorders, including Blau syndrome and early-onset sarcoidosis, are characterized by formation of non-caseating granulomas in different organs, including the eye [12]. Ocular involvement in those cases may be extremely severe, including granulomatous uveitis that may affect both anterior and posterior segment, with vitritis, chorioretinitis, and optical neuritis [13].

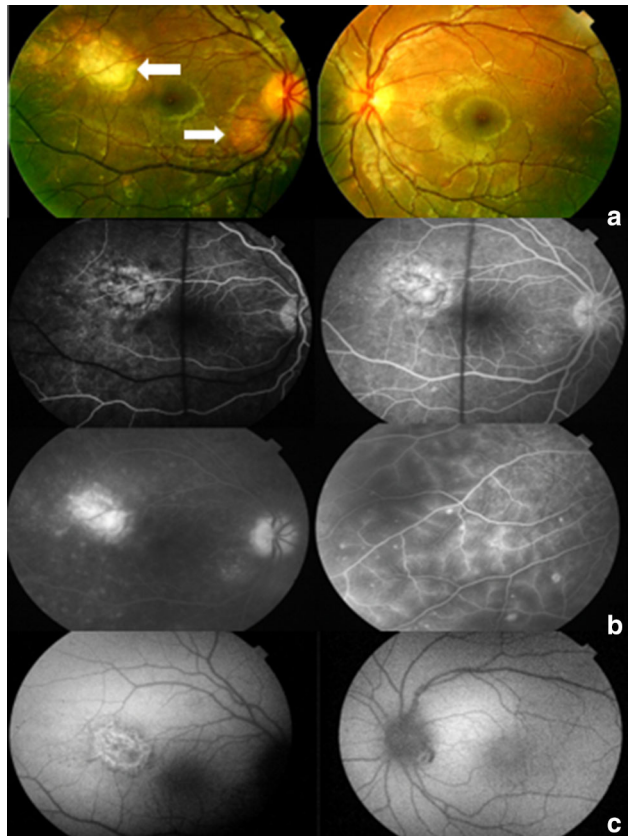

Fig. 1 Examination at the initial visit. **a** Fundus examination revealed two yellow creamy lesions (arrows) in the posterior pole of the right eye. **b** Active lesions on fluorescein angiography of OD, with early hypofluorescence and late hyperfluorescence, late disk staining, and widespread peripheral capillary leakage. **c** Hyper-autofluorescent lesion on the autofluorescent fundus OD

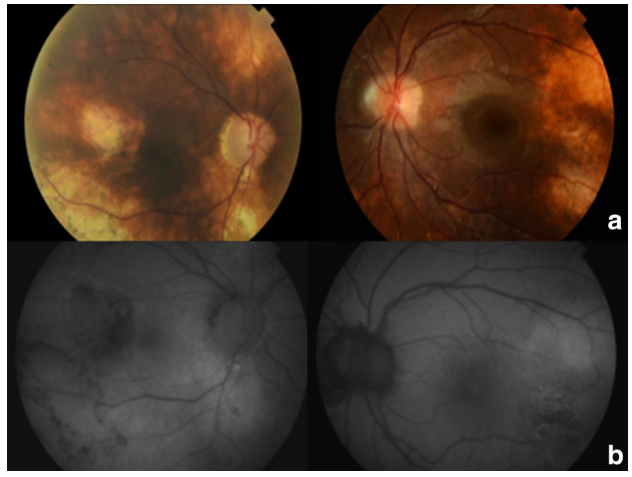

Fig. 2 Examination 32 months after the initial visit. **a** Fundus examination showed larger but atrophic-inactive retinal lesions OU. **b** Hypo-autofluorescent lesions on the autofluorescent fundus OU

This clinical picture is similar to our patient's case, as it constitutes a severe and bilateral uveitis that starts by involving the anterior chamber with extensive synechiae formation, and in subsequent months, develops yellowish elevated lesions that may correspond to choroidal granulomas. In the report of the international registry of Blau syndrome, 87% of the patients had intraocular inflammation. All of the patients developed anterior chamber inflammation, and posterior segment involvement was present in up to 77% [14].

On the other hand, as far as we know, intraocular inflammation has not been described in TRAPS. A series of 25 patients with a clinical and molecular diagnosis of TRAPS was reported by Toro et al. [15], who showed that 44% had ocular involvement, consistent in conjunctivitis and periorbital edema. Lachman et al. [10] have reported the largest TRAPS series to date, which included 158 patients, of whom 20% showed periorbital edema, and 22% had signs of acute conjunctivitis. Interestingly, their study demonstrated that ocular involvement was less frequent in patients carrying the low-penetrance mutation R92Q [10]. Additionally, in some cases, patients with TRAPS have demonstrated central nervous system involvement [16].

Our patient carried this R92Q mutation, which is the most common TNFRSF1A variant, found in 34% of cases [10]. There is still not consensus of whether this is a low-penetrance variant, a functional polymorphism, or a susceptibility factor for inflammation [5]. This mutation is usually characterized by a milder and more variable symptomatology, which is not true in the present case, shorter duration of attacks, and lower risk of amyloidosis [17, 18].

Conclusions

This is the first case reported of panuveitis related to TRAPS. For cases of uveitis of unknown etiology, genetic analysis is extremely important to establish an adequate diagnosis and treatment. This is especially critical in children, where uveitis is potentially vision-threatening, and the diagnosis is often challenging.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Additionally, informed consent was obtained from all individual participants included in the study.

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