Am J Transl Res 2022;14(12):8768-8772
www.ajtr.org /ISSN:1943-8141/AJTR0147013

Brief Communication

Association of bilateral pan-uveitis with the use of trametinib for Langerhans cell histiocytosis

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Received October 14, 2022; Accepted November 25, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Targeted therapy has expanded our current treatment options for various diseases including Langerhans cell histiocytosis. However, side effects associated with targeted therapy should be recognized and addressed. In this study, we report a pediatric bilateral pan-uveitis associated with the use of trametinib for Langerhans cell histiocytosis. A 10-year-old boy with Langerhans cell histiocytosis that was being treated by trametinib presented with mutton-fat keratic precipitates, anterior chamber cells, hyperemic swelling discs, subretinal fluid, and choroidal edema in both eyes. He was diagnosed with pan-uveitis in both eyes. When the trametinib therapy was stopped, the symptoms disappeared after local and systematic corticosteroid treatment. In conclusion, MEK (mitogen-activated protein/extracellular signal-related kinase kinase) inhibitor trametinib treatment alone might be associated with ocular toxicity presenting as Vogt Koyanaki Harada syndrome-like pan-uveitis. Ocular symptoms and signs should be monitored carefully during MEK inhibitor therapy.

Keywords: Trametinib, pediatric pan-uveitis, VKH-like disease, Langerhans cell histiocytosis

Introduction

The mitogen-activated protein kinase (MAPK) pathway is a key signaling pathway involved in many cellular processes, including cell proliferation, differentiation, survival, and motility [1]. Activating mutations of the MAPK pathway have been reported to play important roles in the occurrence and progression of cancer as well as other diseases such as Langerhans cell histiocytosis (LCH) [1, 2]. The most common MAPK pathway mutation in LCH is *BRAF* p.V600E mutation [2]. Trametinib is an oral, highly selective MEK1/2 (MAP/ERK (extracellular signal-related kinase) kinase 1/2) inhibitor of the MAPK signaling pathway, which has been not only used in the treatment of BRAF mutation-harboring melanoma and non-small cell lung cancer, but also used in the treatment of LCH, alone or in combination with BRAF-inhibitors [3]. Although complete remission has been reported in LCH patients treated with trametinib [4, 5], the ocular side effects associated with this targeted therapy, presenting as anterior or pan-uveitis, serous retinal detachments, multifocal choroiditis, or retinal vein occlusion, are important to consider. In this report, we present a pediatric bilateral pan-uveitis associated with the use of trametinib for the treatment of Langerhans cell histiocytosis.

Methods

Data about the patient were extracted from the medical records of Beijing Tsinghua Changgung Hospital. The patient underwent visual acuity (VA) test, fundus color photography, optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) and ultrasound B scan at the first and follow-up visits, as per the routine protocol in our center. PubMed, Embase, and Web of Science were searched up to October 14, 2022 for literature review.

Result

A 10-year-old boy visited our hospital who complained of blurry vision for 12 days; however, he didn't have ocular irritation, pain, floating,

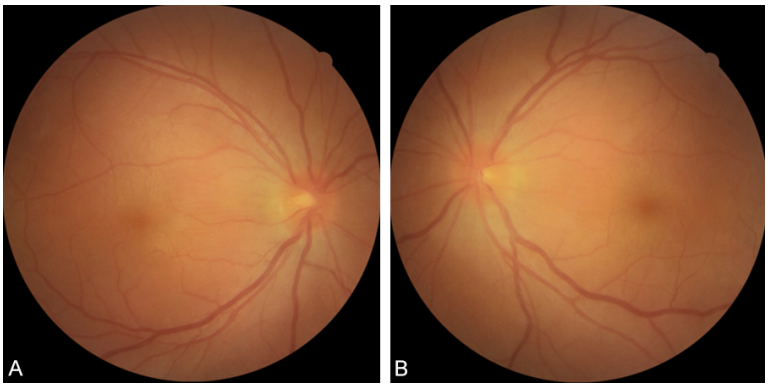

Figure 1. Fundus examination of both eyes. Fundus examination of the right eye (A) and the left eye (B) showed bilateral hyperemia, blurred margin of the optic disc, and retinal folds in the posterior pole.

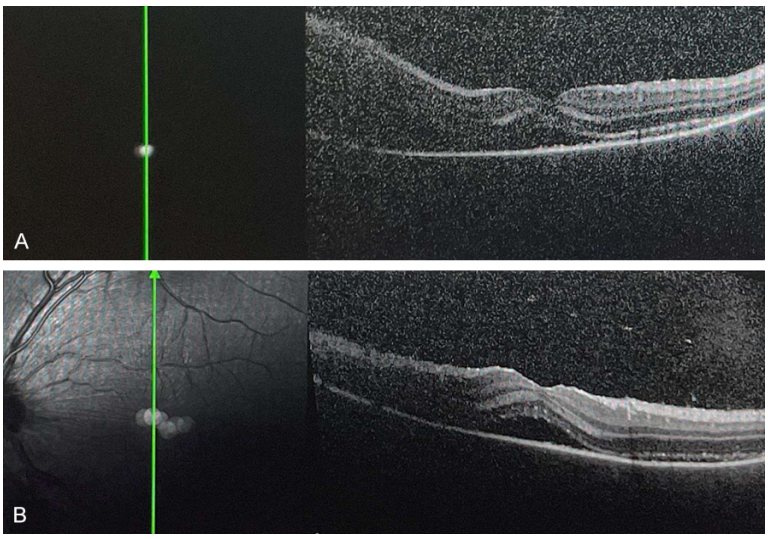

Figure 2. Spectral-domain optical coherence tomography (SD-OCT). Right eye (A) and left eye (B) SD-OCT showed subretinal fluid in the macula.

headache, flu-like syndrome, hearing loss, or vitiligo. He had a history of Langerhans cell histiocytosis for 8 years and had started oral trametinib (0.5 mg) treatment daily 26 days prior, but stopped the treatment 3 days before the hospital visit. Other past medical history was normal. The child received serologic tests for syphilis, hepatitis virus B and C, AIDS, toxoplasma, rubella, cytomegalovirus, herpes simplex virus, and tuberculosis in another hospital before trametinib treatment and were all negative.

His uncorrected visual acuity was 2/20 for both eyes and he was found to have a refraction of -6.50/-0.50 × 165 with the corrected acuity of $12/20^{-2}$ in the right eye and -6.00 with the corrected acuity of 8/20 in the left eye. Non-contact tonometry was 12.6 mmHg in the right eye and 17.3 mmHg in the left eye. The slit lamp examination showed diffuse mutton-fat keratic precipitates, 3+ anterior chamber cells, and anterior chamber flare in both eyes. His conjunctiva, cornea, iris, and pupillary light reflex were normal in both eyes. Fundus examination revealed bilateral hyperemia, blurred margin of the optic disc, and retinal folds in the posterior pole (**Figure 1**). Optical coherence tomography (OCT) presented bilateral subretinal fluid in the macula (**Figure 2**). Ultrasound B scan reported choroid thickening in both eyes (**Figure 3**). Ultrasound biomicroscopy (UBM) reported ciliary body edema in both eyes. This patient was not able to undertake fluorescein angiogram because of an allergic reaction to the fluorescent dye.

To alleviate the symptoms, the patient was treated with bilateral periocular injection of dexamethasone (2.5 mg) for one time, topical prednisolone eight times a day, pranoprofen four times a day, and atropine twice a day for a week. Yet, the visual acuity of both eyes was still 2/20 although keratic precipitates, anterior chamber cells, and flare had disappeared. In support of this, the OCT showed that the subretinal fluid was not reduced markedly. Therefore, the patient was given oral methylprednisolone (48 mg) daily for three days. Significantly, his visual acuity was improved to 5/20 in the right eye and 3/20 in the left eye. The OCT showed that the subretinal fluid was partially absorbed. Oral methylprednisolone was then reduced to 40 mg daily for a week. At the end of this treatment, his visual acuity was improved to 8/20 for both eyes, and subretinal fluid was absorbed in both eyes as shown in the OCT. Hence, the local steroid treatment was stopped, while the oral ste-

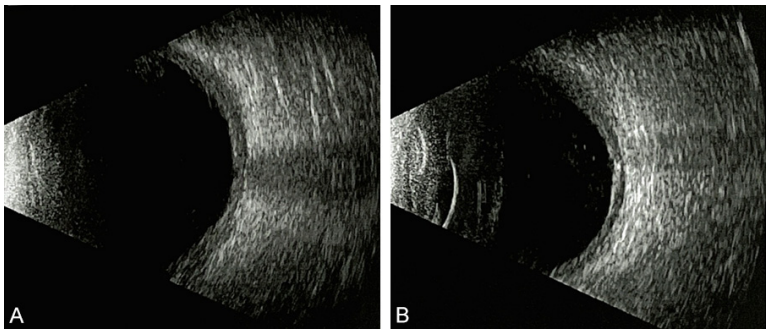

Figure 3. Ultrasound B scan. Ultrasound B scan of right eye (A) and left eye (B) reported choroid thickening in both eyes.

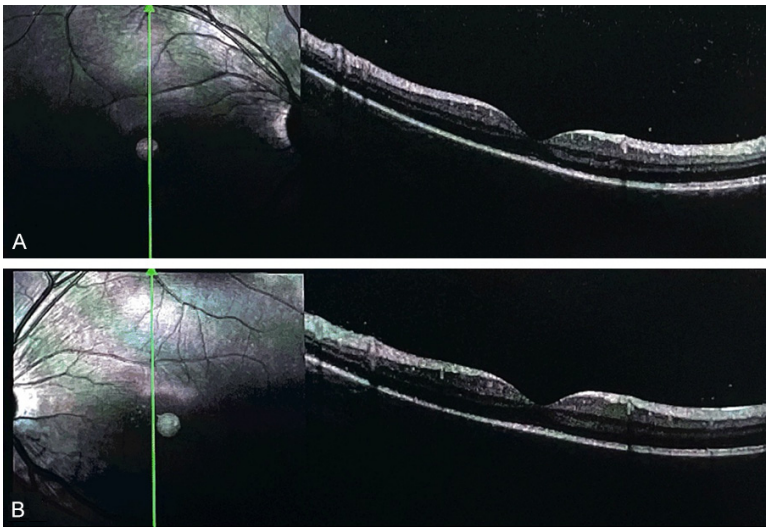

Figure 4. Spectral-domain optical coherence tomography (SD-OCT) at 3 weeks after treatment. SD-OCT of the right eye (A) and the left eye (B) at 3 weeks after treatment showed that the subretinal fluid was completely absorbed, while there was some disruption in the interdigitation and ellipsoid zone.

roid was continued for another week, which improved his visual acuity to 6/20 corrected to 14/20 in the right eye and 12/20 corrected to 16/20 in the left eye. In addition, anterior chamber inflammation, subretinal fluid, and choroidal edema had all disappeared (**Figure 4**).

Discussion

In this paper, we report our treatment strategy for a Vogt Koyanaki Harada syndrome-like pan-uveitis associated with the use of trametinib in a 10-year-old patient with Langerhans cell histiocytosis. To the best of our knowledge, this was the youngest LCH patient reported experiencing a MEK inhibitor treatment-associated ocular adverse effect.

The MAPK signaling pathway plays critical roles in the pathogenesis of various cancers, including cutaneous melanoma, thyroid carcinoma, colorectal adenocarcinoma, and lung adenocarcinoma. During MAPK signal transduction, extracellular signals are transduced through the protein kinase cascade by activating rapidly accelerated fibrosarcoma (RAF), MEK, and ERK to regulate the expression of target genes [6]. The importance of MAPK signaling activity in disease development can be reflected by the fact that BRAF mutations are commonly seen in various diseases including LCH [7]. LCH is a disease with abnormal accumulation of a particular immune cell type, histocytes. The genomic analysis of LCH reveals the existence of BRAF, MEK, and other MAPK pathway component mutations, which provides a rationale for inhibiting MEK as a treatment strategy for this disease [5, 8-11]. Accordingly, trametinib, a selective MEK1/2 inhibitor, has been reported to be effective in the treatment of LCH [4, 5, 12]. However, ocular adverse side effects in this group of patients have not been fully described. Although ocular adverse effects of targeted therapy in asymptomatic patients can be quite high [13], in different phases of cancer clinical trials, trametinib treatment showed 10% to 15% ocular toxicity, and mostly showed mild symptoms [14, 15]. Nevertheless, moderate to severe ocular toxicity included posterior uveitis, pan-uveitis, retinal vein occlusion, and MEK inhibitor-associated retinopathy (MEKAR). Some of these effects may be temporary, while others might cause irreversible vision loss [16].

Furthermore, several cases of VKH syndrome-like pan-uveitis after dabrafenib/trametinib therapy for cutaneous melanoma were previously reported. For example, Lim et al. reported a 61-year-old male with mutton-fat keratic pre-

cipitates, anterior chamber cells, no vitreous cells, hyperemic swelling discs, and subretinal fluid in both eyes following treatment [17]. Brambati et al. reported a 53-year-old man with mutton-fat keratic precipitates, 3+ cells in the anterior chamber, posterior synechiae, hyperemic disc, and multiple yellowish bullous serous retinal detachments in both eyes [18]. Additionally, Fujimura et al. reported two cases of patients aged 35 and 73 with VKH syndrome-like ocular manifestation as well as hearing loss and vitiligo [19]. They also possessed HLA-DRB1*04:05, which was strongly associated with VKH disease. In our study, we reported a 10-year-old male who presented with mutton-fat keratic precipitates, anterior chamber cells, hyperemic swelling discs, subretinal fluid, and choroidal edema in both eyes. The molecular mechanism underlying the development of these adverse effects is not fully understood. One hypothesis is that MAPK inhibition might lead to a retinal pigment epithelial lesion, thus causing a blood retinal barrier breakdown, while it has been proposed that shared antigens in melanocytes of melanoma and of the choroid might induce a cross-autoimmune reaction, which is not supported by our LCH patient [17, 20]. Targeting the immune response is a possible treatment strategy for these side effects as the autoimmune responses in these patients were enhanced by trametinib treatment. Previously reported cases, above all, received oral or intravenous corticosteroid treatment and visual acuity increased from hand motion to 20/25 [17-19].

For the treatment of this 10-year-old patient, since stopping trametinib did not improve ocular manifestation, we applied local and systemic steroids to the patient and closely monitored the possible side effects of steroid use in children. Although there is a growing awareness of ocular adverse effects during targeted therapy, it is important to recognize that there can be rare but sight-threating toxicities, and it is necessary for ophthalmologists and oncologists to communicate for the treatment and education of the patient.

Conclusion

Treatment using MEK inhibitor trametinib may be associated with ocular toxicity presenting as Vogt Koyanaki Harada syndrome-like pan-uveitis. Ocular symptoms and signs should be monitored carefully during trametinib therapy.

Acknowledgements

The authors certify that they have obtained the patient's consent form. The patient and his relative have given their consent for the patient's clinical information to be reported in this journal while their personal information, such as names, initials or any information that might reveal their personal identity, will not be mentioned or published.

Disclosure of conflict of interest

None.

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