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CLINICAL CASE REPORT

Vogt-Koyanagi-Harada syndrome-like uveitis after nivolumab administration as a treatment for ovarian cancer

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Abstract
Purpose To report a case of Vogt-Koyanagi-Harada (VKH) syndrome-like posterior uveitis after nivolumab administration to treat an ovarian cancer with an electrophysiological finding.
Case summary A 61-year-old woman with ovarian cancer (stage 3A) and salpingo-oophorectomy surgery history visited the clinic complaining of blurred vision in both eyes. She had been enrolled a clinical trial using nivolumab in patients with ovarian cancer. She received four cycles of nivolumab administration and experienced blurred vision one week before the initial visit. There was no remarkable finding in the anterior segment and the vitreous body. Multiple subretinal fluid accumulations and serous retinal detachment were identified on the posterior pole. Subretinal fluid with choroidal folding was noted in optical coherence tomography, and multiple leakage points were also observed in wide-field fundus fluorescein angiography. Therefore, intravenous high-dose steroid pulse therapy was applied under the diagnosis of VKH syndrome-like posterior uveitis induced by an immunotherapy agent. After steroid therapy, the subretinal fluid was absorbed completely, and the patient's visual acuity was recovered to the normal range. The amplitudes in the multifocal electroretinogram were also restored after the treatment.
Conclusion Nivolumab is a human IgG4 monoclonal antibody and an immune checkpoint inhibitor. It is associated with the upregulation of T-cell activity by interfering with the interaction between the programmed death-1 (PD-1) receptor and the PD-ligand. Targeted therapy using immunotherapy agents has been widely used for malignant melanoma, lung cancer, renal cell carcinoma, and other cancers. However, immunotherapy agents such as nivolumab can induce autoimmune-related adverse events including uveitis. This report suggests that VKH syndrome-like posterior uveitis could be induced by nivolumab administration for an ovarian cancer treatment, which was resolved by steroid pulse therapy.

Keywords Immunotherapy agent · Multifocal electroretinogram · Nivolumab · Steroid · Vogt-Koyanagi-Harada syndrome-like uveitis

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Introduction

Vogt-Koyanagi-Harada (VKH) syndrome is characterized by bilateral diffuse granulomatous uveitis

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[1, 2]. In addition, patients with VKH syndrome usually experience neurologic and auditory symptoms such as headache and tinnitus before the uveitis period, and dermatologic symptoms such as poliosis, vitiligo, and alopecia after the uveitis period [1]. The suggested mechanism of VKH syndrome is inflammation induced by an autoimmune reaction against melanocytes [1, 2]. Recently, wide-spread targeted therapy using immunotherapy agents including immune checkpoint inhibitors for the cancer patients was reported to induce immune-related adverse events such as uveitis [3].

Nivolumab is a human immunoglobulin G4 monoclonal antibody, which blocks the human programmed death protein-1 (PD-1) receptor. It is a kind of immune checkpoint inhibitor and has been used for first-line treatment or maintenance treatment for various types of cancer [4–7]. Here, we report a patient with an electrophysiological finding, who developed VKH syndrome-like bilateral posterior uveitis after nivolumab administration as a treatment for ovarian cancer.

Case report

A 61-year-old woman was referred to the ophthalmology department from the gynecologic oncology division of the obstetrics and gynecology department. She complained of blurred vision in both eyes, with symptoms has beginning one week earlier. She underwent a hysterectomy with salpingo-oophorectomy two years ago due to ovarian cancer stage 3A. Six cycles of chemotherapy using a combined regimen of paclitaxel and carboplatin were performed. However, the chemotherapy was discontinued because the patient experienced general weakness and a reduction in the absolute neutrophil count. Therefore, she was enrolled in a clinical trial using nivolumab for patients with ovarian cancer as maintenance therapy (A Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy, ATHENA Trial). She had already received four cycles of nivolumab administration at a dose of 2 mg/kg at 4-week intervals before the initial visit. She did not have any other documented medical history such as hypertension or diabetes mellitus.

At the initial visit to the ophthalmology department, her best correct visual acuity (BCVA) was 20/20, despite subjective blurring symptoms in both eyes. At that time, the patient experienced mild headache. Intraocular pressure was within the normal range, and there was no remarkable finding in the anterior segment or vitreous body. Optic disk edema with choroidal swelling on the posterior pole was found in both eyes in the fundus examination (Fig. 1a, b). Optical coherence tomography (OCT) showed choroidal folding without an accumulation of subretinal fluid (SRF) (Fig. 1c, d). Additionally, choroidal thickening was also identified in OCT scan images. Brain magnetic resonance imaging (MRI) with contrast enhancement was performed to rule out optic neuritis and a metastatic lesion to the periocular area, which revealed no remarkable findings.

The patient revisited after 1 week, complaining of worsening blurring in both eyes. The BCVA was reduced to 20/100 in the right eye and 20/40 in the left. The intraocular pressure and anterior segment findings showed no remarkable changes compared to the findings one week earlier. However, multiple SRF collections were identified on the posterior pole and serous retinal detachment (SRD) was observed on the inferior and nasal retina (Fig. 1e, f). Massive SRF accumulation with choroidal folding was noted in OCT scan, and choroidal thickening was exacerbated (Fig. 1i,j). Multiple leakage points of fluorescein dye with optic disc staining were also observed in the late phase in wide-field fundus fluorescein angiography (FFA) (Fig. 1g, h). Therefore, intravenous high-dose steroid pulse therapy was applied for the patient under the diagnosis of VKH syndrome-like posterior uveitis induced by an immunotherapy agent. Prednisolone was administered every six hours (1000 mg/day) for three days intravenously, and oral prednisolone was provided with tapering. Nivolumab administration was stopped, and withdrawal from the clinical trial was confirmed. Human leukocyte antigen (HLA) examination could not be performed because the patient refused.

After steroid therapy, SRF which was observed in the OCT was completely absorbed, and visual acuity was recovered to 20/20 after two months. The SRF in the left eye disappeared within one month after the therapy (Fig. 2j), while that in the right eye was absorbed completely after two months (Fig. 2e). Moreover, choroidal folding was resolved, and

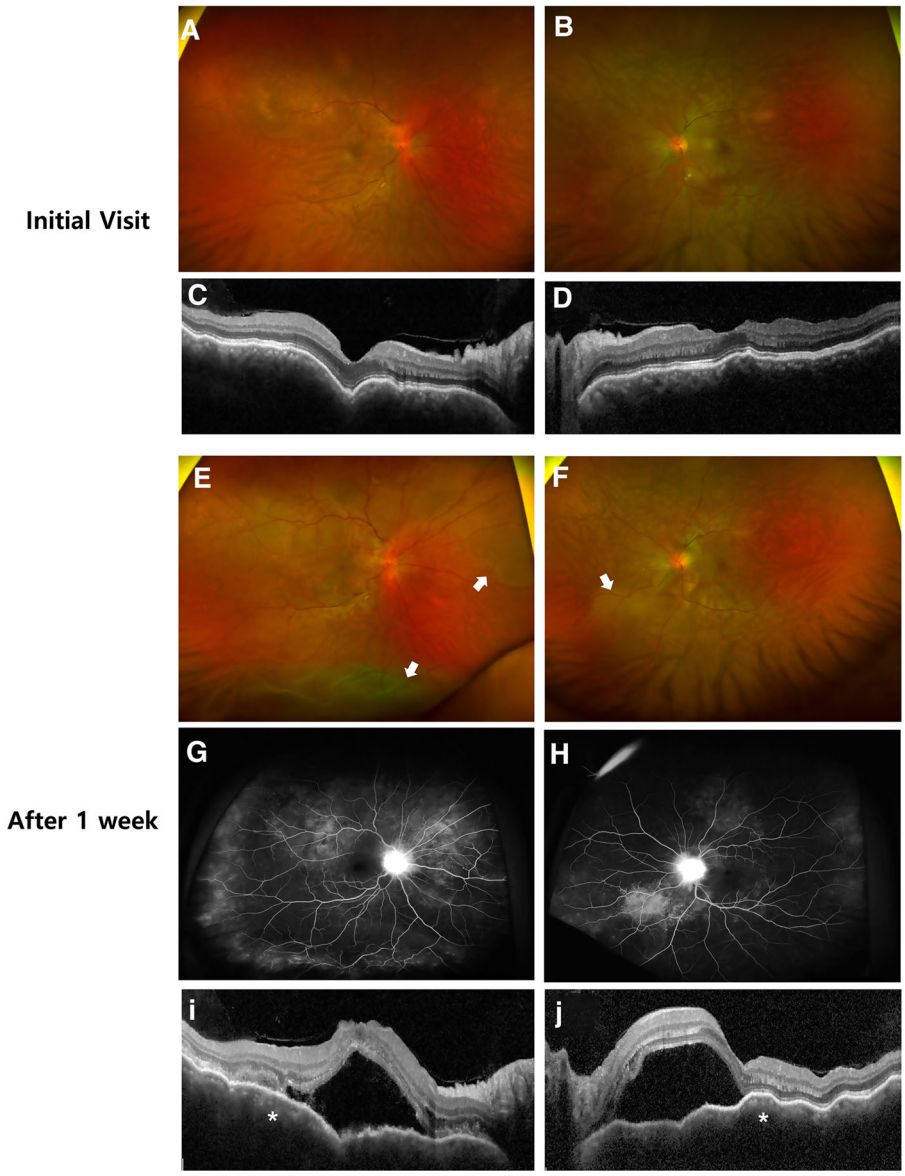

Fig. 1 Clinical manifestations of a 61-year-old woman with Vogt-Koyanagi-Harada syndrome-like uveitis after nivolumab administration as a treatment for ovarian cancer. At the initial visit, disc swelling was found in both eyes (**a**, **b**), and choroidal folding without subretinal fluid (SRF) accumulation was identified by optical coherence tomography (OCT) (**c**, **d**). However, her visual acuity was reduced after one week and serous retinal detachments (arrows) were shown in both eyes (**e**, **f**). Multiple leakages of fluorescein with optic disc staining were observed at the late phase in the wide-field fundus fluorescein angiography (**g**, **h**). Massive SRF accumulation with choroidal folding was noted in both eyes, and marked choroidal thickening was also identified (**i**, **j**, asterisks)

thickness of the choroid was reduced one or two weeks after steroid therapy (Fig. 2c, h). Disruption of ellipsoid zone (EZ) in the parafoveal area was still observed in the left eye 4 months after the treatment, while EZ in the fovea was recovered in the right eye (Fig. 2f, l). The visual acuity of the patient was maintained for four months without the recurrence of VKH syndrome-like posterior uveitis.

The SRD in the inferior retina of the right eye was resolved for four months after steroid pulse therapy (Fig. 3a–d). Moreover, the SRD in the nasal retina in the left eye was also absorbed after the therapy

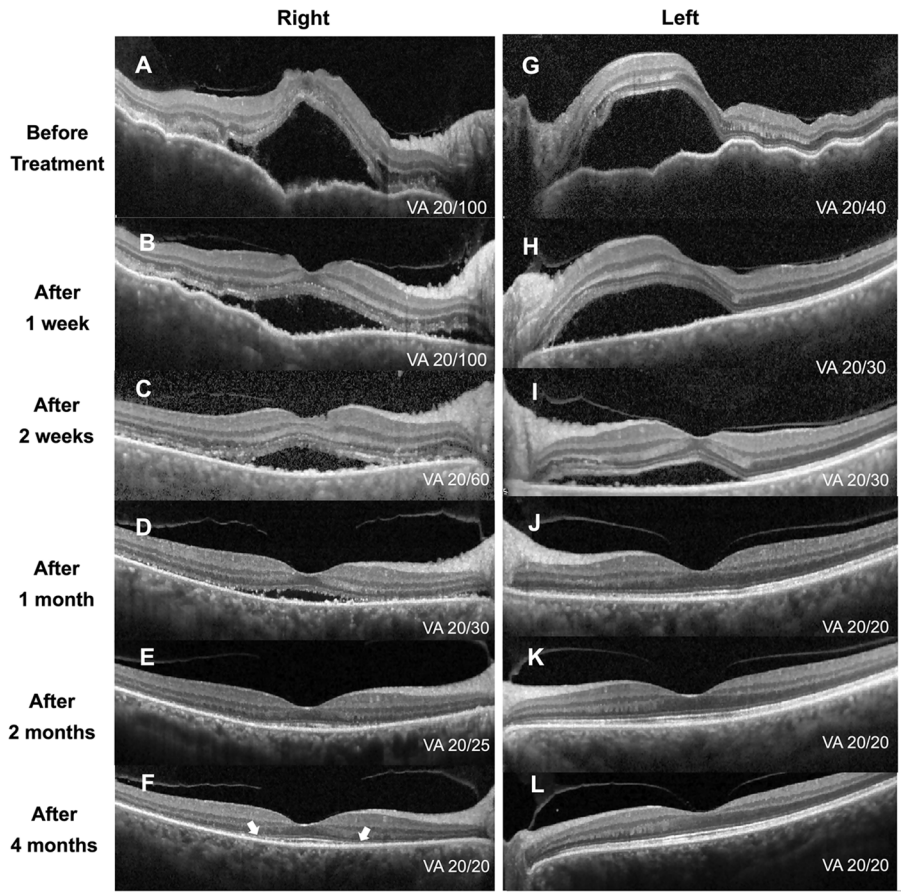

Fig. 2 Consecutive changes in the OCT scan images of the patient with VKH syndrome-like uveitis after nivolumab administration. After the steroid pulse therapy, the SRF in the right eye was completely absorbed, and visual acuity was recovered to the normal range after two months (**a** to **f**). The SRF in the left eye disappeared within one month after the therapy (**g** to **l**). In addition, choroidal folding was resolved on one or two weeks after the steroid therapy (**c**, **h**). The visual acuity of the patient was maintained for four months without the recurrence of VKH syndrome-like posterior uveitis (**f**, **l**). Disruption of ellipsoid zone in the parafoveal area was still observed in the left eye after the treatment (**f**, arrows), while EZ was recovered in the right eye (**l**). VA; visual acuity

(Fig. 3e–h). Depigmented lesions of the retina pigment epithelium, such as sunset glow appearance, were not identified without recurrence of the uveitis after four months (Fig. 3d, h). Moreover, the patient did not experience poliosis and vitiligo, which were common sequelae observed in typical VKH syndrome patients after the uveitis phase.

A multifocal electroretinogram (mfERG) was also performed before and after steroid therapy to objectively evaluate the retinal function of the patient. The first-order kernel mfERG responses were elicited using MonPack One® (Metrovision, Perenchies, France), and the recording of mfERG was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) Standard for mfERG [8]. Prior to mfERG recording, the eyes were light-adapted for 15 min in room light, and recording was achieved using contact lens electrodes (ERG jet®, Fabrinal SA, La Chaux-de-Fonds, Switzerland) after full pupil dilation. The stimulus which was consisted of an array of 61-scaled hexagon-based pattern was presented on an LCD monitor. The luminance of the bright hexagon was maintained at 100 cd/m^2, while that of the dark hexagon was < 1 cd/m^2. The stimulus frequency was set at 17 Hz. The bandpass of the filters was 3–100 Hz, and amplification was performed with a gain of 105. Fixation stability was continuously monitored with a mounted infrared camera during the

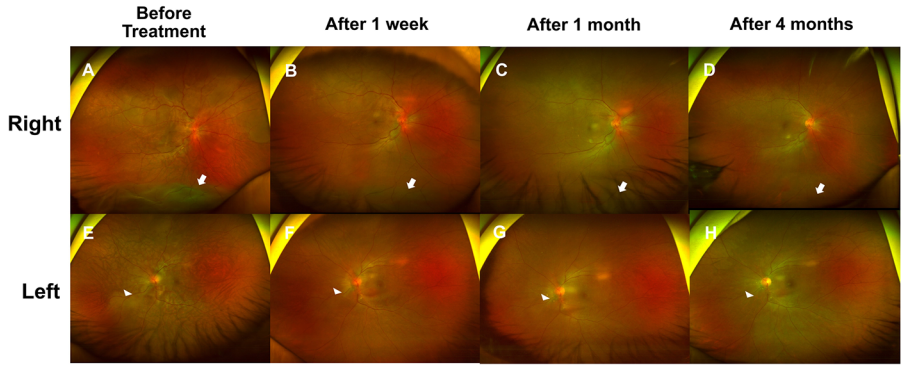

Fig. 3 Consecutive changes in the fundus findings of the patient with VKH syndrome-like uveitis caused by nivolumab administration. Serous retinal detachment in the inferior retina (arrows) of the right eye was resolved four months after the steroid pulse therapy (**a** to **d**). Serous retinal detachment (arrowheads) in the nasal retina in the left eye was also absorbed after the therapy (**e** to **h**). Depigmented lesion of the retina pigment epithelium of the retina such as sunset glow appearance was not identified without the recurrence of the uveitis after four months (**d**, **h**)

recording. The mfERG results including the amplitudes and implicit times of the P1 and N1 responses were evaluated.

Reductions in the N1 and P1 amplitudes in mfERG were obvious in both eyes before steroid therapy, in which the right eye was more deteriorated (Fig. 4a, e) (Table 1). Before steroid therapy, the amplitudes of N1 in the ring 1 of mfERG in the right and left eyes were − 188 and − 540 nV, respectively. The amplitudes of P1 were 486 nV in the right eye and 1199 nV in the left, respectively. The implicit times were also elongated initially (Table 1). The restoration of the amplitudes in both eyes was induced by steroid pulse therapy (Fig. 4) (Table 1). After the therapy, the amplitudes of N1 in the ring 1 of mfERG in the right and left eyes were recovered to − 554 and − 939 nV, respectively. The amplitudes of P1 were 1172 and 1717 nV, respectively, four months after steroid therapy (Table 1). In addition, the implicit times were also gradually recovered in both eyes after the therapy (Table 1). However, the macular function of the right eye remained decreased even four months after the therapy, compared to the left eye (Fig. 4d) (Table1). The amplitudes of N1 and P1 waves in more eccentric rings were also reduced. The amplitudes were increased after the treatment, while those were still lower after 4 months of the treatment, compared to the normal range.

After four months of steroid therapy, the oral administration of prednisolone with tapering was discontinued, and uveitis did not recur for six months. The ovarian cancer of the patient did not recur after stopping nivolumab treatment, and the patient has been regularly followed up by the gynecology and ophthalmology departments.

Discussion

Nivolumab is an immune checkpoint inhibitor, which blocks the PD-1 receptors of the T-cells [9]. It induces the upregulation of T-cell immunologic activity and contributes to the interaction with antigen-presenting cells such as dendritic cell [9, 10]. Therefore, nivolumab has been used as a targeted therapy for various cancers including malignant melanoma, lung cancer, squamous cell head and neck cancer, Hodgkin lymphoma, retinal cell carcinoma, and hepatocellular carcinoma [4–7, 9, 11]. Moreover, nivolumab can be used in combination therapy with other monoclonal antibodies, tyrosine kinase inhibitors or poly-ADP ribose polymerase (PARP)-1 inhibitors.[12–14]

Conventional chemotherapy agents induce various common side effects including infection, bleeding tendency, anemia, hair loss, nausea, vomiting, gastrointestinal problems, skin rash, and neuropathic pain. Recently, immunotherapy agents have been widely used for inoperable or metastatic cancers, and even used as first-line anti-cancer therapy [4–7, 9, 14]. Immunotherapy agents are known to induce fewer side effects than conventional chemotherapy [3, 9]. Furthermore, some immunotherapy agents including nivolumab have been applied as maintenance therapy

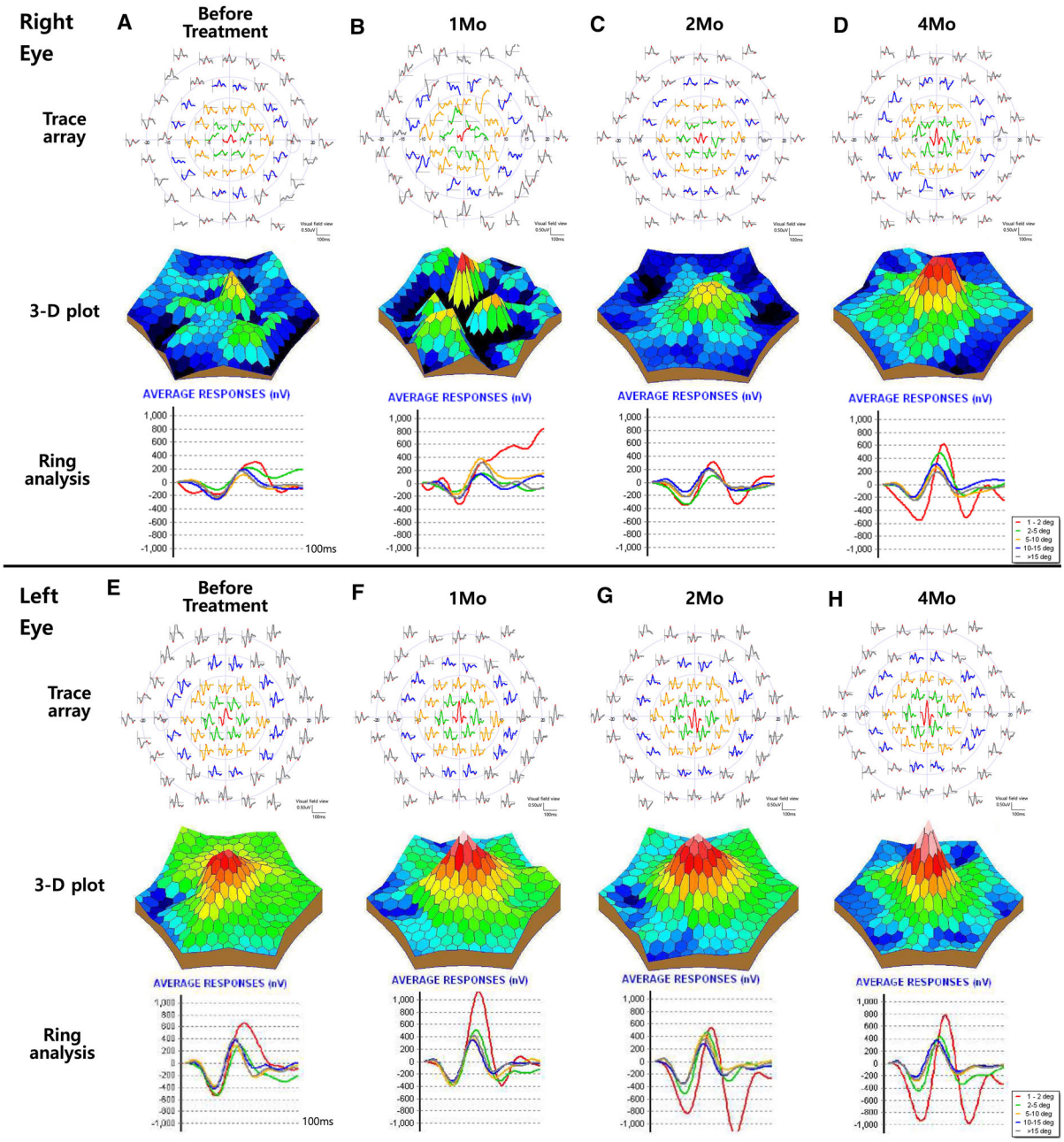

Fig. 4 Consecutive changes in the multifocal electroretinogram (mfERG) findings including the results of trace array, 3-D plot, and ring analysis, which was performed before and after the steroid therapy to objectively evaluate the retinal function of the patient. Reductions in the mfERG response were obviously in both eyes at the initial visit (**a**, **e**), in which the right eye was more deteriorated (**a**). Restorations of the responses in the right (**a** to **d**) and the left eyes (**e** to **h**) followed the steroid pulse therapy. However, the macular function of the right eye remained decreased four months after steroid therapy, compared to the left eye (**d**, **h**)

followed by a first-line chemotherapeutic agent [6, 15].

Nevertheless, immunotherapy agents also can induce several side effects in the patients. The common and minor side effects of the immunotherapy

Table 1 Consecutive changes of amplitudes and implicit times in the ring 1 of mfERG from the patient with VKH syndrome-like uveitis after nivolumab administration

Period	Right		Left	
	N1 (nV)	P1 (nV)	N1 (nV)	P1 (nV)
Before steroid therapy	− 188	486	− 540	1199
After 1Mo	− 268	578	− 387	1477
After 2Mo	− 355	667	− 832	1370
After 4Mo	− 554	1172	− 939	1717
Period	Right		Left	
	N1 (ms)	P1 (ms)	N1 (ms)	P1 (ms)
Before steroid therapy	34.0	63.1	29.3	53.6
After 1Mo	27.8	51.9	28.4	49.1
After 2Mo	29.9	51.6	28.1	46.4
After 4Mo	28.6	48.7	28.9	46.9

agents are fatigue, cough, skin rash, muscle pain, liver problems, and reduced numbers of white blood cells.[16] Most of the severe adverse events by immunotherapy agents are immune-related complications because these agents have an effect on the upregulation of the immune activity of the patients. Hepatitis, colitis, thyroiditis, and pneumonitis due to autoimmune mechanisms were reported after the use of immunotherapy agents.[17] In addition, skin eruptions and kidney problems can follow immunotherapy agent administration including nivolumab [16, 17]. These immune-related adverse events may become more frequent as the immunotherapy agents become more widely used.

The occurrence of uveitis after the administration of immunotherapy agents, which is also known as pharmacologically induced uveitis or drug-induced uveitis, was also reported previously [18]. It is known that not only nivolumab but also other immunotherapy agents can induce immunotherapy-associated uveitis. Previous studies reported the association of vemurafenib, dabrafenib, trametinib, ipilimumab, and pembrolizumab with pharmacologically induced uveitis [18]. It was noted that nivolumab seemed to have an incidence of uveitis of approximately 6% in malignant melanoma patients [16–19]. The exact mechanism of uveitis, including VKH syndrome-like uveitis, after the administration of immunotherapy agents is still unclear. It is assumed that uveitis can be induced by autoimmune mechanism, which is increased by immune response from upregulated T-cell activity after nivolumab administration. Therefore, the activated T-cells may target the normal melanocytes of uveal tissue in the patient [20].

VKH syndrome-like uveitis was observed after nivolumab administration in several case reports. Matsuo et al. showed a VKH syndrome-like panuveitis with a severe anterior chamber reaction and a sunset glow appearance after nivolumab administration for malignant melanoma [20]. Kikuchi et al. also noted massive SRF accumulation with large pigment epithelial detachment on OCT scans due to VKH syndrome-like uveitis and a sunset glow appearance after the recovery of uveitis signs [21]. Fujimura et al. reported on a VKH syndrome-like posterior uveitis patient with transient hearing loss and vitiligo [22]. Obata et al. also presented a patient with VKH syndrome-like posterior uveitis after nivolumab administration for malignant melanoma [23]. In that report, the OCT scan revealed choroidal folding with SRF, similar to this case. The onset of VKH syndrome-like uveitis was from the second to the fourth cycle of nivolumab administration. In addition, a patient with malignant melanoma treated with pembrolizumab also developed VKH syndrome-like uveitis [24]. Enomoto et al. recently presented a case with subretinal fluid resolution and electrophysiologic improvement after discontinuation of the agent and steroid replacement therapy [24]. Furthermore, all of the patients in the previous reports and the patient in this case report were Asian.

In this case, the patient had multiple fluid collections with peripapillary retinal swelling in the fundus examination. Furthermore, multiple hyperfluorescent points by leakage were identified by the FFA. The fundus and FFA findings of this patient were similar to those of typical VKH syndrome patients. In contrast, the OCT scan image of VKH syndrome-like uveitis caused by nivolumab was relatively different from that of typical VKH syndrome. A septation structure between the SRF-collected space was not found in this patient, and choroidal folding was more prominent than in typical VKH syndrome patients. These findings were consistent with the previous papers on VKH syndrome-like uveitis by immunotherapy agents [20–24]. Moreover, SRF accumulation and choroidal folding were completely resolved without atrophic changes on the OCT scan image after the steroid therapy [20–24].

Steroid therapy after stopping nivolumab administration is generally recommended as a treatment modality for the VKH syndrome-like uveitis patients. Topical, subtenon injection, and systemic steroid administrations were effective for the visual impairment recovery and SRF resolution in the patients. The recurrence of VKH syndrome-like uveitis after steroid therapy has not been reported [20–24]. In this case, steroid pulse therapy achieved a restoration of visual acuity to the normal range and the complete absorption of SRF within two months. The favorable visual prognosis of VKH syndrome-like uveitis patients induced by nivolumab was the same as in the previous reports [20–24].

To investigate the recovery of retinal function periodically, mfERG was performed on the patient from the initial visit. Enomoto et al. reported that flicker ERGs in full-field ERG were helpful in monitoring retinal function before and after the steroid treatment in a patient with VKH syndrome-like uveitis developed by an immunotherapy agent [24]. On the other hand, mfERG was conducted in this case in order to evaluate the recovery of macular function especially. Macular function, which is evaluated by mfERG, was also gradually improved after steroid pulse therapy for four months. In the left eye, the amplitude was restored to the normal range two months after steroid therapy, whereas the amplitude in the right eye still showed reduced response density four months later. It is thought that the recovery of the amplitude in the right eye was relatively slower than in the left eye because of the large amount of SRF accumulation in the initial period and remnant disruption of EZ in the parafoveal area at 4 months after the treatment. There was asymmetric bilateral abnormality in mfERG parameters and OCT findings in this patient. The discrepancy of mfERG findings between both eyes was also identified in another previous report [24]. It is believed that the response density of mfERG in the right eye of this patient will recover to the normal range after a few months later.

The amplitudes of N1 and P1 waves in more eccentric rings, except ring 1, were also reduced (Fig. 4a, e). Functional impairment in eccentric rings was more severe in the right eye of the patient. Like a macular function, the functional recovery of paramacular area was also identified after the treatment; however, the paramacular function was still impaired after 4 months of the treatment in the right eye (Fig. 4d, h).

mfERG has been used to evaluate the macular function in the patients with VKH syndrome in a few studies [25, 26]. The amplitudes of mfERG were associated with ellipsoid zone integrity on OCT scan image and visual field parameters [26]. The changes of mfERG findings of the patient with VKH syndrome-like uveitis by nivolumab were similar with typical VKH syndrome patients. In typical VKH cases, markedly reduction in the amplitudes of N1 and P1 waves was also observed before the treatment, and the amplitudes were increased following prompt treatment [25]. However, recovery of amplitudes was started one or three months after the treatment, and significantly lower amplitudes of both N1 and P1 waves were still found at 12 months after the treatment, compared to normal control group [25]. In contrast, the recovery of amplitudes in the patient with VKH syndrome-like uveitis by nivolumab started earlier, compared to typical VKH syndrome cases [25]. In addition, the N1 and P1 amplitudes of the left eye of the patient reached the normal range after 4 months. Earlier start for recovery of macular function of VKH syndrome-like uveitis by nivolumab was a different point in mfERG findings from typical VKH patients. It is suggested that these points can be associated with good visual prognosis in this patient.

There were two limitations in this report. First, this is a single case report of VKH syndrome-like uveitis caused by nivolumab. Second, HLA serotyping was not performed. Further researches about anatomical

and functional recovery of VKH syndrome-like uveitis induced by other immunotherapy agents including nivolumab with large population are needed in the future.

In summary, immunotherapy agents for anti-cancer therapy such as nivolumab can induce various autoimmune-related complications including uveitis. Nivolumab can be associated with bilateral panuveitis, and the clinical manifestations are similar to those of VKH syndrome. VKH syndrome-like uveitis caused by nivolumab occurred after the second to fourth cycles of administration. The OCT findings, which showed prominent choroidal folding and a lack of septation, were different from those of typical VKH syndrome patients. However, steroid pulse therapy was effective for resolution of the SRF accumulation, recovering visual acuity, and improving retinal function, which is similar to the results of treating typical VKH syndrome. Macular function which evaluated using mfERG was markedly reduced before treatment, and that was increased after prompt treatment including discontinuation of nivolumab and steroid therapy. Restoration of mfERG and OCT findings was identified in the left eye after four months after the treatment. Conversely, reduced mfERG amplitudes and EZ disruption were remained in the right eye of the patient, though BCVA was recovered to the normal range. Moreover, recovery of the mfERG findings started in both eyes at earlier period after the treatment, compared typical VKH syndrome cases. The patient with VKH syndrome-like uveitis caused by nivolumab had a favorable visual prognosis without sequelae and recurrence after the steroid therapy.

Due to the widespread usage of immunotherapy agents for cancer patients, the number of patients with autoimmune-related complications including VKH syndrome-like uveitis may increase in the future. The probability of pharmacologically induced uveitis such as VKH syndrome-like uveitis should be considered in a patient with visual impairment during the anti-cancer therapy using immunotherapy agents.

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Declarations

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

Ethical approval All procedures performed in this case report involving a human participant were in accordance with the ethical standards of Declaration of Helsinki and its later amendments or comparable ethical standards. This report was approved by institutional review board (IRB) of Soonchunhyang University Cheonan Hospital (IRB File No. 2020–12-041).

Statement of human rights All procedures performed in this case report involving a human participant were in accordance with the ethical standards of the Soonchunhyang University Cheonan Hospital and with the Declaration of Helsinki and its later amendments.

Statement on the welfare of animals This report does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from the participant included in this case report.

References

1. Moorthy RS, Inomata H, Rao NA (1995) Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 39(4):265–292
2. Sakata VM et al (2014) Diagnosis and classification of Vogt-Koyanagi-Harada disease. Autoimmun Rev 13(4–5):550–555
3. Dalvin LA et al (2018) Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina 38(6):1063–1078
4. Ferris RL et al (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375(19):1856–1867
5. Motzer RJ et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373(19):1803–1813
6. Robert C et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372(4):320–330
7. Finkelmeier F, Waidmann O, Trojan J (2018) Nivolumab for the treatment of hepatocellular carcinoma. Expert Rev Anticancer Ther 18(12):1169–1175
8. Hood DC, et al (2012) ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol 124(1):1–13
9. Brahmer JR et al (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366(26):2455–2465
10. Lin H et al (2018) Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade-mediated tumor regression. J Clin Invest 128(2):805–815
11. Armand P et al (2018) Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. J Clin Oncol 36(14):1428–1439
12. Khaddour K et al (2021) Mutation clearance and complete radiologic resolution of immunotherapy relapsed metastatic melanoma after treatment with nivolumab and olaparib in a

patient with homologous recombinant deficiency: any role for PARP inhibitors and checkpoint blockade? Ann Oncol 32(2):279–280
13. Kudo M (2020) Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. Cancers (Basel) 12(5)
14. Paz-Ares L et al (2021) First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol 22(2):198–211
15. Zamarin D et al (2020) Randomized phase II Trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study. J Clin Oncol 38(16):1814–1823
16. Xu C et al (2018) Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ 363:k4226
17. Agrawal L et al (2020) Immune checkpoint inhibitors and endocrine side effects, a narrative review. Postgrad Med 132(2):206–214
18. Abdalla Elsayed MEA, Kozak I (2021) Pharmacologically induced uveitis. Surv Ophthalmol
19. Wolchok JD et al (2013) Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369(2):122–133
20. Matsuo T, Yamasaki O (2017) Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma. Clin Case Rep 5(5):694–700
21. Kikuchi R, Kawagoe T, Hotta K (2020) Vogt-Koyanagi-Harada disease-like uveitis following nivolumab administration treated with steroid pulse therapy: a case report. BMC Ophthalmol 20(1):252
22. Fujimura T et al (2018) HLA-DRB1*04:05 in two cases of Vogt-Koyanagi-Harada disease-like uveitis developing from an advanced melanoma patient treated by sequential administration of nivolumab and dabrafenib/trametinib therapy. J Dermatol 45(6):735–737
23. Obata S et al (2019) Vogt-Koyanagi-Harada disease-like uveitis during nivolumab (anti-PD-1 antibody) treatment for metastatic cutaneous malignant melanoma. Case Rep Ophthalmol 10(1):67–74
24. Enomoto H et al (2021) Case with metastatic cutaneous malignant melanoma that developed Vogt-Koyanagi-Harada-like uveitis following pembrolizumab treatment. Doc Ophthalmol 142(3):353–360
25. Yang P et al (2008) Study of macular function by multifocal electroretinography in patients with Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 146(5):767–771
26. Souto FMS et al (2021) Associations between functional and structural measurements in non-acute Vogt-Koyanagi-Harada disease. Acta Ophthalmol 99(5):e715–e723