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Case Report

Sight-Threatening Immune Retinopathy Developing Secondary to Durvalumab Treatment of Small-Cell Lung Cancer: A Case Report

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Keywords

Cancer-associated retinopathy · Durvalumab · Immune checkpoint inhibitor · Immune retinopathy

Abstract

Introduction: Given the recent additions of immune checkpoint inhibitors (ICIs) to various cancer treatments, adverse effects, especially involving the eyes, have been on the rise. Here, we report an acute exacerbation of cancer-associated retinopathy (CAR) triggered by durvalumab treatment of small-cell lung cancer (SCLC). ***Case Presentation:*** An 81-year-old Asian male complained of a scotoma in the left eye after durvalumab administration, to treat SCLC. Humphrey visual field examination revealed a C-shaped temporal scotoma. Spectralis domain optical coherence tomography revealed outer retinal layer atrophy and progressive loss of the ellipsoid zone in the atrophic peripapillary area. Fundus autofluorescence (AF) images evidenced a large C-shaped hypo-AF with enhanced AF at the margin of the atrophic area, thus at the position of the scotoma. We prescribed subtenon triamcinolone injections under suspicion of CAR exacerbation, supported by positive Western blotting results for Rab6 and aldolase, and immunohistochemical staining of photoreceptor cells. The disrupted ellipsoid zone evident on OCT partially recovered, and a visual field test showed that the scotoma had improved. ***Conclusion:*** ICI-triggered exacerbation of CAR should be considered in SCLC patients before ICI treatment commences; an optimal treatment should preserve functional vision.

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Introduction

It is increasingly evident that immune checkpoint inhibitors (ICIs) improve the survival of patients with a variety of solid malignancies, including small-cell lung cancer (SCLC). ICIs currently feature prominently in solid cancer chemotherapies. Thus, the differential diagnosis of cancer-associated retinopathy (CAR) and autoimmune retinopathy caused or aggravated by ICIs has become of concern. ICIs inhibit the production of checkpoint proteins by certain immune and cancer cells. Immune checkpoint proteins such as programmed death-ligand 1 (PD-L1) on cancer cells and programmed cell death 1 (PD-1) on immune cells interact to prevent T cells from killing cancer cells. Antibodies (Abs) to checkpoint proteins can help restore the immune system, allowing cancer cell killing [1]. ICIs are treatment options for advanced-stage SCLC. Some studies have suggested that immunotherapy combined with chemotherapy should be the new standard treatment for advanced-stage SCLC [2, 3].

Durvalumab (Imfinzi, AstraZeneca) inhibits the PD-L1-PD-1 interaction. The US Food and Drug Administration (FDA) rapidly approved durvalumab for patients with extensive-stage-SCLC [4] given the few other effective therapeutic options for advanced cancers. Although these inhibitors are effective against previously formidable cancers, their rapid approval prevented complete evaluation of possible side effects. Amplification of the immune response may increase the risk of immune-related adverse effects (irAEs); retinal vasculitis is a known side effect of durvalumab [5]. The absence of PD-L1 signaling by retinal pigment epithelial cells may allow PD-1-positive T cells to infiltrate the inflamed vascular wall and release effector cytokines [6].

Durvalumab-induced secondary retinal vasculitis in a non-SCLC patient was reported in 2020 [5]. However, that patient evidenced macular edema with retinal vascular sheathing; our present case exhibited progressive photoreceptor atrophy. In the Republic of Korea, no durvalumab-related ocular side effects have yet been reported in individuals with SCLC. We thus present the rare case of a patient with stage IV SCLC who developed photoreceptor atrophy in both eyes after durvalumab treatment.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538246).

Case Presentation

On an unscheduled visit, an 81-year-old Korean male complained of a new symptom: a temporal C-shaped scotoma in the left eye that had commenced 2 months prior his fifth cycle of anti-PD-L1 treatment. He had been on regular follow-up in our outpatient clinic for 3 years after multiple anti-vascular endothelial growth factor injections to treat neovascular age-related macular degeneration (nAMD) of his right eye. The last injection into the right eye was 9 months prior. He had a history of type 2 diabetes and hypothyroidism. He had been diagnosed with advanced SCLC (T2b/3, N3, M1a) 5 months ago and had received durvalumab (1,500 mg) chemotherapy at 3-week intervals. The visual acuity was 20/100 in the right eye and 20/20 in the left on the last regular follow-up of nAMD, thus before anti-cancer treatment. The non-proliferative diabetic retinopathy in both eyes and the nAMD in the right eye were under control.

At the time of the new complaint, the visual acuity had fallen to 20/200 in the right eye and 20/25 in the left eye, but with normal intraocular pressures. The anterior segment was clear. The right fundus photograph revealed an atrophic macula attributable to the nAMD, and there was no specific finding in the left eye other than mild pigmentary changes (Fig. 1a). On fundus autofluorescence (AF) examination, photoreceptor injuries evidenced by broad C-shaped hypo-AFs with hyperfluorescent margins explained the symptoms in both eyes

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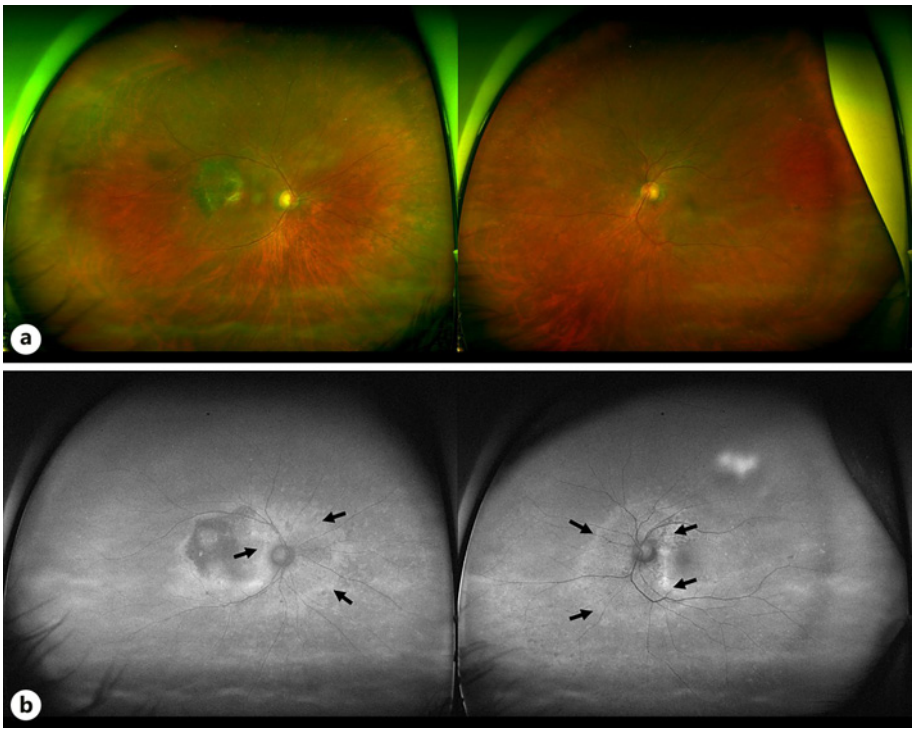

Fig. 1. a Fundus photograph showed atrophic macula due to previous nAMD treated with multiple anti-vascular endothelial growth factor (anti-VEGF) injections in the right eye, and no pathognomonic sign was found except floater in the left eye. **b** Fundus AF revealed large C-shaped hypo-AF with enhanced AF at the margins in both eyes (black arrowheads).

(Fig. 1b). Optical coherence tomography (OCT) revealed loss of the peripapillary retinal ellipsoid zones of the left eye, consistent with a visual field defect (Fig. 2, 3). Fluorescein angiography revealed normal vascular perfusion.

The routine laboratory tests, including complete blood cell count and kidney function, were normal, except for a slight elevation of liver enzyme (AST/ALT). The abdominal ultrasound showed a moderate fatty liver. Thyroid function tests indicated subclinical hypothyroidism with normal T3 and T4, and TSH elevation. The infectious test results, including hepatitis B, hepatitis C, syphilis, and human immunodeficiency virus, were negative. F-fluorodeoxyglucose PET/CT revealed pleural seeding, multiple lymph node metastasis of both paratracheal, aortocaval, and Lt. neck level IV. On brain MRI, Lt. superior frontal gyrus metastasis was noted.

The oncology department was consulted because the bilateral vertical hemianopia raised a suspicion of a central nervous system abnormality such as a brain metastasis of lung cancer. Thorough brain magnetic resonance imaging did not explain the perimetric findings. During close follow-up, the symptoms worsened, and OCT revealed progressive photoreceptor atrophy approaching the fovea of the left eye (Fig. 4) and enlargement of the bilateral temporal scotomas on perimetric examinations (Fig. 3a). Electroretinograms revealed cone and rod cell dysfunctions of the right eye and cone cell dysfunction of the left eye (Fig. 5).

The ellipsoid zone loss evident on OCT progressed rapidly after the lung cancer diagnosis and commencement of chemotherapy, implying that the loss was caused by either the tumor or chemotherapy (online suppl. Table S1). CAR attributable to durvalumab toxicity was suspected. The ocular immunology laboratory of the Casey Eye Institute of the Oregon Health & Science University (OR, USA) performed Ab tests for CAR based on the strong clinical suspicion of CAR or paraneoplastic syndrome. Ocular irAEs are usually treated with corticosteroids, either topically,

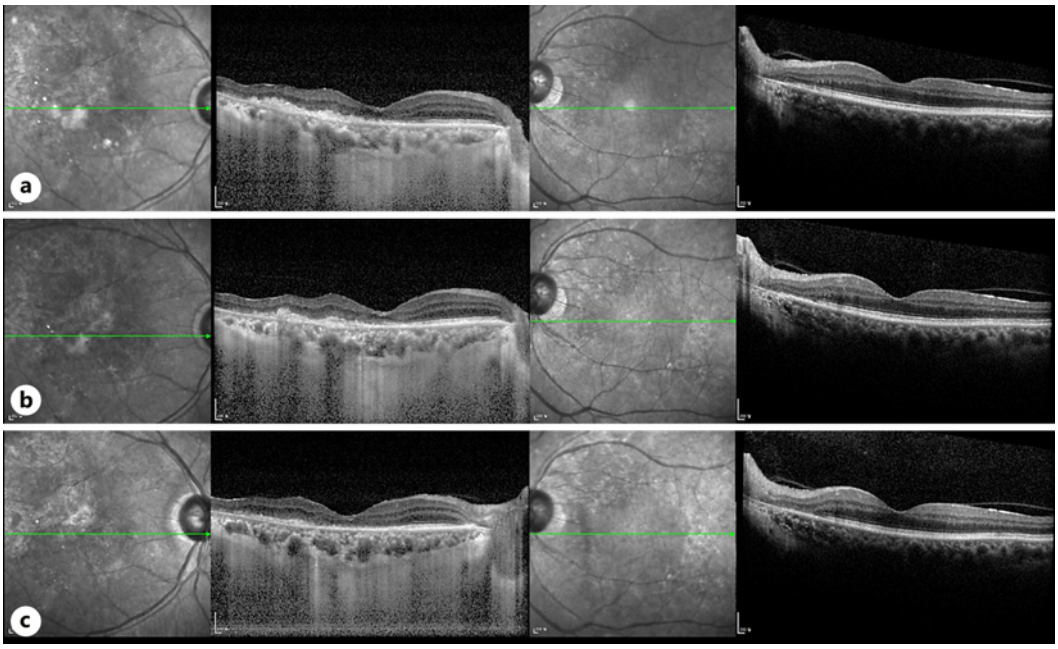

Fig. 2. a Before the durvalumab therapy, OCT showed age-related macular degeneration (AMD)-related macular changes in the right eye and normal findings on the left eye. **b** One month after starting durvalumab, OCT showed mild outer layer atrophy and ellipsoid disruption at nasal retina and temporal to the disc on the left eye. **c** After 6 months of follow-up, OCT showed bilateral outer retinal layer atrophy and progressive loss of ellipsoid line at nasal retina and temporal to the disc in the left eye sparing the fovea corresponding to patient's complaints and visual field examination results.

intraocularly, or systemically, and as the patient was both diabetic and old, he was prescribed only subtenon injections of 4 mg triamcinolone (Dong Kwang Pharm Co. Ltd.).

The Rab6 and aldolase assays were positive, combined with moderate immunohistochemical staining of the retinal photoreceptor outer segment/inner segment, but all of the recoverin, carbonic anhydrase II, enolase, HSP60, TULP1, and GAPDH assays were negative (online suppl. Table S2). After consulting the oncology department, immunochemotherapy was discontinued. Four months after subtenon triamcinolone administration and durvalumab cessation, OCT revealed that the ellipsoid zone near the nasal retina had partially recovered in the left eye (Fig. 3b), and a visual field test revealed a slight decrease in the scotoma sizes of both eyes, associated with symptom improvement (Fig. 4b). However, the outer retinal atrophy re-progressed 6 months after the initial administration of triamcinolone and cessation of durvalumab. Subtenon injections of 4 mg triamcinolone were repeated for both eyes (Fig. 3c, 4c). After the second triamcinolone injection, there was no progression of outer retinal atrophy for 3 months. However, the malignancy worsened, and the patient was unable to visit the outpatient clinic for 5 months (Fig. 3d, 4d). Six months after the second triamcinolone treatment, he again presented with serious visual impairments in both eyes. Despite chemotherapy, the lung cancer had worsened, prompting the oncologist to prescribe nivolumab (OPDIVO, Ono Pharmaceutical Co. Ltd.).

He experienced visual field constrictions in both eyes after 2 months on nivolumab. The visual field test revealed near-total defects in both eyes, and OCT revealed broad, outer retinal atrophy and extensive loss of the ellipsoid zones of both eyes. Only the foveal ellipsoid zone of the left eye was spared. Fundus AF revealed increased hypo-AF at the sites of the earlier C-shaped lesions (Fig. 6). Thereafter, his health deteriorated further, rendering additional follow-up examinations impossible.

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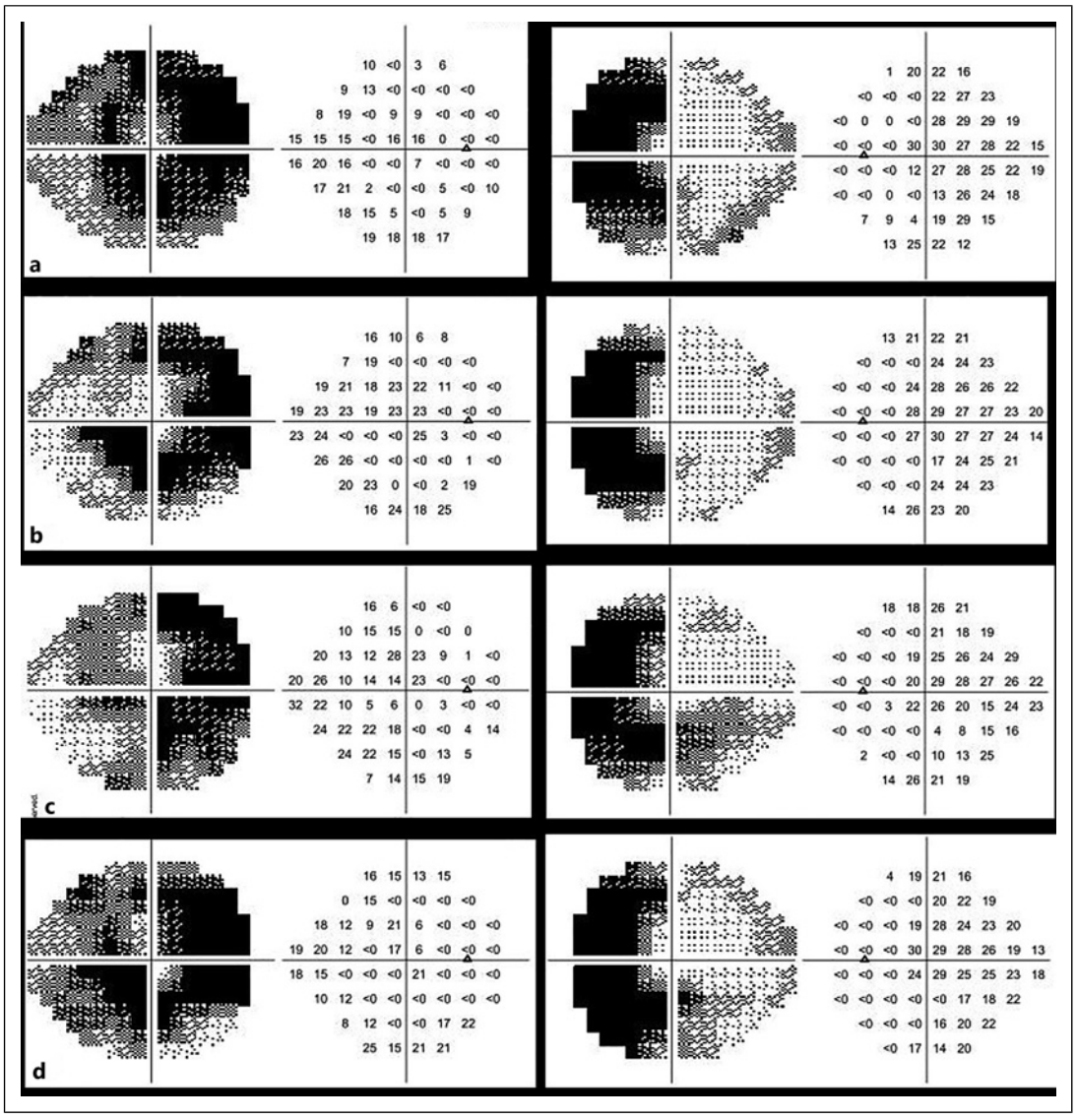

Fig. 3. a Static perimetry of the patient showed central scotoma due to previously treated nAMD in the right eye and mid-peripheral C-shaped scotomas at bilateral visual fields. **b** Four months following visual field examination after stopping durvalumab represented minimal improvement of mid-peripheral scotomas. **c** Six months after ceasing the medication, progressive mid-peripheral scotomas were presented in the left eye. **d** Nine months after quitting medication, static perimetry showed slightly decreased scotomas in the left eye.

Discussion

This is the first Asian case of progressive photoreceptor atrophy after durvalumab treatment of SCLC. The patient complained of a sudden visual scotoma after SCLC diagnosis and durvalumab treatment. As the patient had been continuously followed up in our clinic in terms of his nAMD and diabetic retinopathy, we had serial OCT data from before and after cancer diagnosis and ICI treatment. As OCT performed after ICI treatment revealed rapid progression of outer retinal atrophy, compared to before treatment, and as the Rab6 and

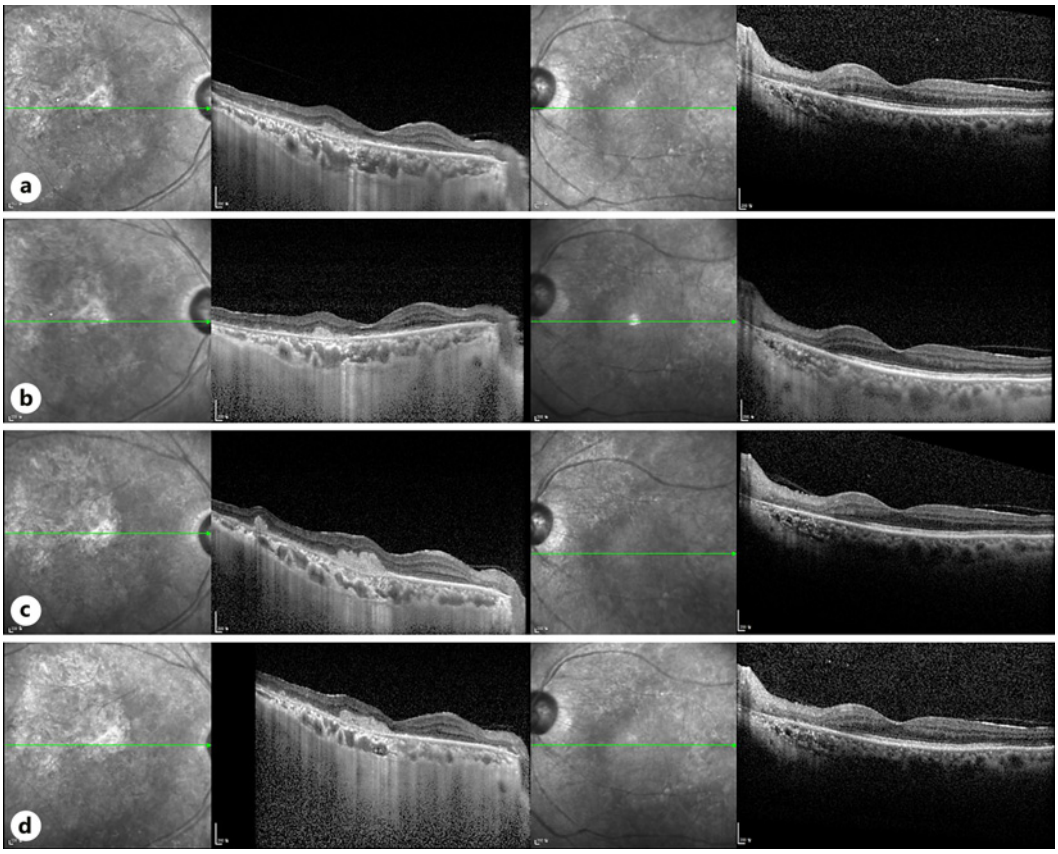

Fig. 4. a After 11 months treated with durvalumab, OCT showed progressive ellipsoid disruption in both eyes. **b** After 4 months of cessation of the medication and treatment with subtenon triamcinolone injection, ellipsoid line at nasal retina was not changed definitely in the left eye. **c** Six months after ceasing the medication, disruption of ellipsoid line was recurred in the left eye and treated with second subtenon triamcinolone injection. **d** After 3 months for second injection, OCT showed no progression of outer retinal atrophy.

aldolase assay results were positive, we suspected acute exacerbation of CAR after ICI treatment [7].

Although the patient had a history of autoimmune disease of hypothyroidism, acute zonal occult outer retinopathy was ruled out because he was elderly and male, and due to the absence of prior symptoms such as a common cold and the absence of photopsia. PD-L1 is expressed by retinal pigment epithelial cells and plays an immunosuppressive role in the posterior eye [8, 9]. Durvalumab, a PD-L1 inhibitor, affects T-cell immunological homeostasis; T cells become hyperactivated when encountering self-antigens. Hyperactivated T cells may target photoreceptor cells, thus explaining the OCT-observed disruptions of photoreceptors and outer segment/inner segment junctions.

Although anti-retinal Abs may be present in normal populations, the incidence of autoantibodies (AAbs) against retinal proteins in retinopathic patients with cancer is higher [10]. Anti-recoverin and anti-enolase AAbs, the most common AAbs in CAR patients [11, 12], were not detected in our patient. Adamus et al. [13] explored the frequencies of AAbs in cancer patient sera. Anti-enolase AAbs were the most common (43%), followed by anti-CAII (28%), anti-GADPH (17%), anti-aldolase C (16%), anti-P62 (15%), anti-arrestin (14%), anti-PKM2 (8%), anti-tubulin (5%), anti-Rab6 (4%), anti-HSP27 (4%), anti-recoverin (3%), and

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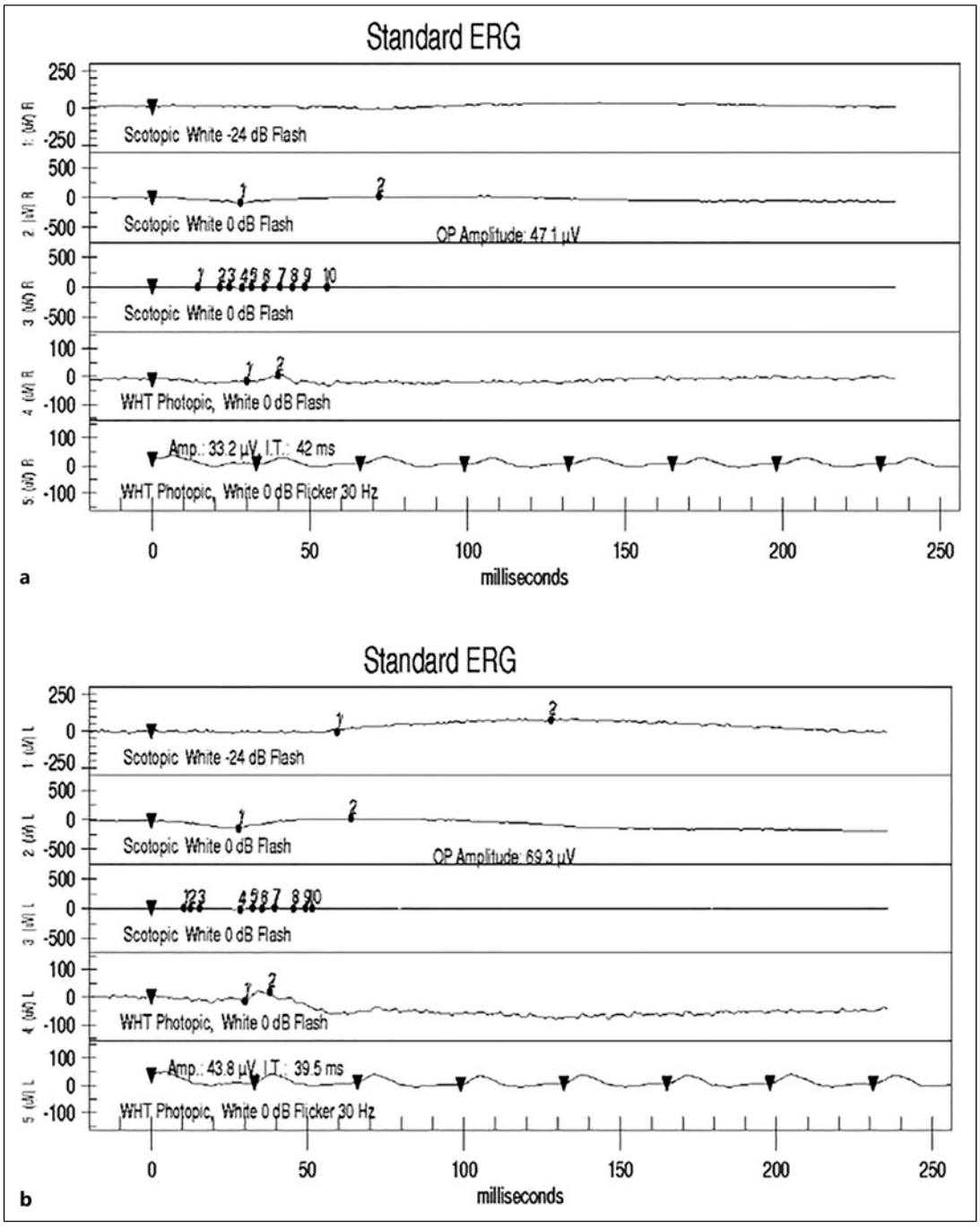

Fig. 5. a, **b** International Society for Clinical Electrophysiology of Vision (ISCEV) protocol using monopolar electrode electroretinograms (ERGs) of patient at time of recognition of bilateral scotoma and 11 months after durvalumab. The results of ERG illustrated dysfunction of cone and rod cell in the right eye and dysfunction of cone cell in the left eye.

anti-CRALBP (3%) Abs. Of 441 CAR patients with AAbs, 16% were positive for anti-aldolase and 5% for anti-Rab6 Abs, compared to 5 and 0% in 127 normal controls.

Rab6 is a photoreceptor that may be involved in CAR pathogenicity [14]. Rhodopsin transport in photoreceptors may be mediated by Rab6; defective trafficking may trigger

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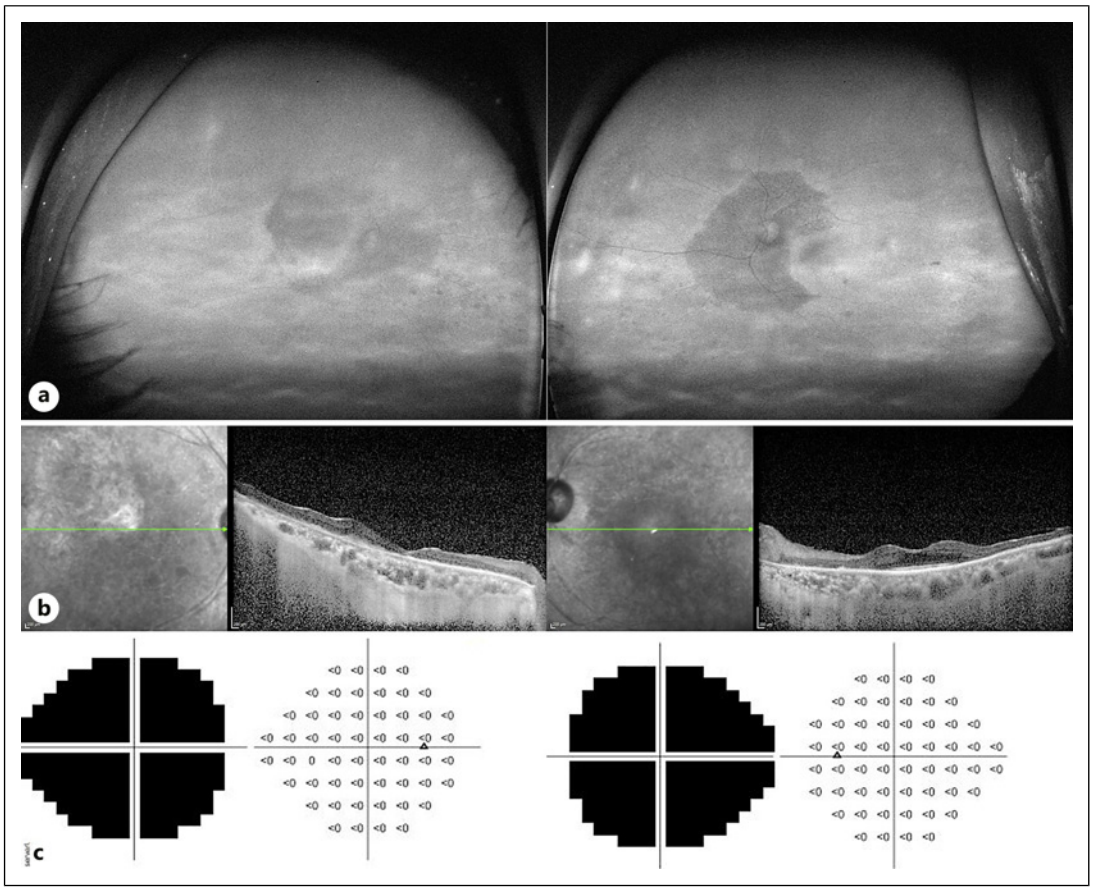

Fig. 6. Examinations after administration of nivolumab. **a** Fundus AF shows definite large C-shaped hypo-AF in both eyes. **b** OCT represents totally atrophic retina in the right eye, progressive loss of ellipsoid line except fovea in the left eye. **c** Static perimetry reveals total scotomas in both eyes.

retinal degeneration [15]. Although anti-aldolase and anti-Rab6 AAbs are not commonly detected in CAR patients, they are absent in healthy individuals. Therefore, it highly suggests that our patient experienced suffering from both CAR and an autoimmune disease.

In one study, the mean time to ocular irAE onset in lung cancer patients was approximately 35 days and the average onset time 57.28 days after ICI commencement [16]. Prior to diagnosis of advanced SCLC, the left eye OCT findings of our patient were stable; however, visual impairment developed 2 months after ICI treatment and rapid advancement of ellipsoid zone disruption was evident on OCT performed 5 months after ICI commencement (Fig. 2a, b). After discontinuation of the ICI and addition of subtenon triamcinolone injections, the symptoms and OCT findings improved (Fig. 3b, d, 4b, d). The response to both durvalumab discontinuation and the periocular steroid injections suggests that the ICI triggered an immune system-mediated retinopathy. Six months after the first steroid injection and discontinuation of durvalumab, retinal atrophy worsened. These serial clinical findings, images and laboratory studies, along with the re-deterioration after treatment with another ICI, suggest that acute durvalumab-mediated CAR exacerbation explains the photoreceptor loss.

Paraneoplastic disorders result from an antitumor immune response against a shared autoantigen between the tumor and ocular tissue. ICI enhances the antitumor immune response, which can lead to increased cross-reaction against ocular structures and unmasking of a predisposed paraneoplastic syndrome [16]. And our findings also suggest that ICI cancer

therapy may exacerbate retinal dysfunction in patients with cancer-related autoimmunity issues. Patients at high risk of CAR should perhaps be tested in terms of retinal AAb status prior to ICI commencement. As durvalumab is the new, standard first-line treatment for extensive-stage-SCLC [2, 4], ICI-induced retinopathy should be considered, especially in patients with preexisting autoimmune diseases and any neuro-ophthalmic complication [17]. Although durvalumab seemed not to induce retinopathy in the CASPIAN study [3], this ICI can trigger irreversible retinal damage. Thus, evaluation of immune-related retinopathy status is important after immunochemotherapy; an optimal treatment should preserve functional vision.

Acknowledgments

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Statement of Ethics

This study followed the tenets of the Helsinki Declaration. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient's son for publication of the details of their medical case and any accompanying images because the patient passed away.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.K., J.K.J., and Y.S. drafted the paper. J.K.J. collected the data, and Y.S. treated the patient. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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