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Cancer-associated retinopathy after anti-programmed death 1 (PD-1) antibody for treating hepatocellular carcinoma——a case report of a Chinese patient

Qian Chen [a], Chaoyi Feng [a], Chuanbin Sun [b], Wenji Wang [a], Min Wang [a,c], Ling Chen [a], Xinghuai Sun [a,c], Guohong Tian [a,c,*]

[a] Department of Ophthalmology, Eye Ear Nose and Throat Hospital, Fudan University, Shanghai, 200031, China
[b] Eye Center, Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, 310009, China
[c] NHC Key Laboratory of Myopia (Fudan University), Key Laboratory of Visual Impairment and Restoration, Shanghai, China

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ABSTRACT

Purpose: Programmed death-1 (PD-1) receptor antibody immune therapy has been widely used for treating solid tumors, and cancer-associated retinopathy after the anti-PD1 treatment have not been reported yet. We report a Chinese patient presenting with acute constriction of visual fields after nivolumab treatment for hepatocellular carcinoma. The diagnosis of cancer-associated retinopathy was confirmed with optical coherence tomography, electroretinography, and positive results for recoverin paraneoplastic antibodies.

Observations: A 57-year-old Chinese man complained of acute visual fields constriction in both eyes for 20 days. He was diagnosed with hepatocellular carcinoma 5 months earlier and treated with chemotherapy for 4 months. He was administered 100 mg of nivolumab as an immune checkpoint inhibitor treatment once every 2 weeks. After 2 cycles of nivolumab, he presented with acute visual problems and was referred to a neuro-ophthalmologist. Brain magnetic resonance imaging excluded optic nerve infiltration and brain metastasis. Optical coherence tomography revealed binocular diffuse loss of outer retinal structures like the circumferential fovea of the macula, and full-field electroretinography showed an almost extinguished response. A serum anti-paraneoplastic antibody panel was positive for anti-recoverin antibodies. He was diagnosed with cancer-associated retinopathy. He was treated with systemic steroids, followed by tryptophan immunoadsorption for 3 cycles. His visual field had slightly improved at a 2-year follow-up.

Conclusions and Importance: Although paraneoplastic retinopathy could be diagnosed in tumor patients, acute-onset vision disturbance after anti-PD-1 treatment might be related to complications of the immune checkpoint inhibitor therapy. Cancer-associated retinopathy, as well as uveitis and optic neuropathy, might arise after anti-PD-1 therapy.

1. Introduction

Immune checkpoint inhibitors, like nivolumab and pembrolizumab, are antibodies against programmed death-1 (PD-1) receptors and are widely utilized for treating solid tumors. These medications can upregulate the immune system and lead to autoimmune-like side effects. The ophthalmic adverse effects include uveitis, dry eye, keratitis, and immune retinopathy.[1,2] We report a Chinese patient who presented with severe visual field constriction after nivolumab treatment for hepatocellular carcinoma. Findings from optical coherence tomography (OCT), electroretinography (ERG), and a serum anti-recoverin antibody test were consistent with a diagnosis of cancer-associated retinopathy (CAR). To our knowledge, this is the first case report of CAR after anti-PD-1 therapy.

2. Case report

A 57-year-old man complained of acute constriction of visual fields

* Corresponding author. Department of Ophthalmology, Eye Ear Nose and Throat Hospital, Fudan University, 83 Fenyang Road, Shanghai, 200031, China.
E-mail addresses: qianchen02@aliyun.com (Q. Chen), lexie.fcy@hotmail.com (C. Feng), sunshine2008@zju.edu.cn (C. Sun), wangwenji@outlook.com (W. Wang), wangmin83@yahoo.com (M. Wang), linglingchen98@hotmail.com (L. Chen), xhsun@shmu.edu.cn (X. Sun), valentian99@hotmail.com (G. Tian).

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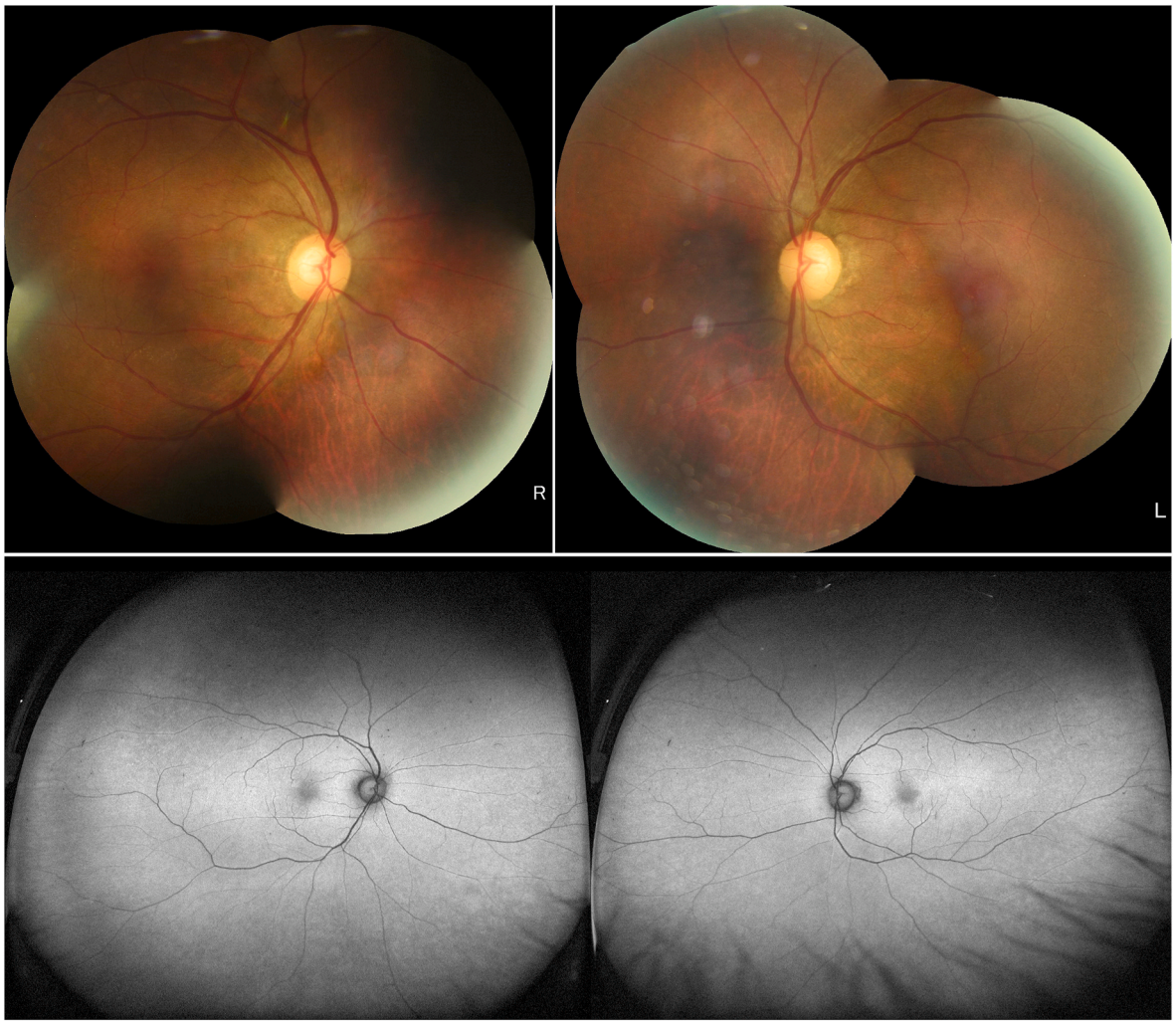

Fig. 1. Fundus photographs (upper panel) and auto-fluorescence (lower panel) of a patient with cancer-associated retinopathy after anti-programmed death 1 (PD-1) antibody showing a normal optic disc with sharp margins without pallor. The retinal vasculature shows slight attenuation without hemorrhage or exudation. The ultra-widefield fundus auto-fluorescence imaging is unremarkable.

in both eyes after his second cycle of anti-PD-1 treatment. He was diagnosed with stage 4 hepatocellular carcinoma 5 months earlier, and he was treated with transarterial chemotherapy for 4 months. He was administered immune checkpoint inhibitor therapy (100 mg nivolumab, once every 2 weeks). He found that his visual fields shrank 2 days after the second cycle of nivolumab treatment, and his ophthalmologist referred him for further neuro-ophthalmology evaluation. He did not experience eye pain, headache, or neurological focal signs. In the following days, it was observed that the constriction of visual fields in both eyes deteriorated very quickly. He did not have any other previous eye problems. He quit smoking and drinking alcohol since the carcinoma was diagnosed. His family history was unremarkable.

The neuro-ophthalmological examination revealed the patient to be alert and oriented. The best-corrected visual acuity score was 20/25 OU. The Ishihara color vision test showed correct identification of 2/8 plates OU. The pupils were equal in size, and no afferent papillary defect was detected. The intraocular pressure was 12 mmHg OD and 11 mmHg OS. There were inflammatory cells in the left vitreous. Funduscopic examination revealed optic discs with sharp margins and normal color with the cup to disk ratio of about 0.4 OD and 0.5 OS for the right and left eye, respectively. Both posterior retinas and maculae were unremarkable (Fig. 1). The lids and extraocular motility were unremarkable. There were no other abnormal neurological focal signs.

Routine laboratory tests were normal for complete blood cell count and liver and kidney function. The infectious panel results, including human immunodeficiency virus, herpes simplex virus, cytomegalovirus, *Treponema pallidum* antibodies, and tests for Tuberculosis (T-spot), were negative. However, the test for the Hepatitis B virus was positive.

Octopus static visual fields (Haag-Streit, Köniz, Switzerland) showed a peripheral defect in the right eye and ring scotomas involving the center field in the left eye, and Humphrey visual field testing one week later showed severe constriction in the right eye and center scotomas (Fig. 2). The visual evoked potential testing showed prolonged P100 latency and decreased amplitude in both eyes. Brain and orbital magnetic resonance imaging with contrast showed normal bilateral optic nerves without enhancement and no other remarkable findings. Fluorescein fundus angiography showed no leakage of fluorescein in the bilateral optic nerves and retina. OCT showed loss of outer retinal structure at the bilateral circumferential foveae of the maculae (Fig. 3). Full-field ERG showed extinguished scotopic and photopic responses (Fig. 4). A serum anti-paraneoplastic antibody panel was positive only for the anti-recoverin antibody. CAR was diagnosed, and intravenous methylprednisolone (250 mg/day) was given for 3 days, followed by tryptophan immunoadsorption for 3 cycles. The best-corrected visual acuity after treatment was 20/20 OU with a slight improvement in the visual fields, whereas the repeated OCT and ERG were almost unchanged. Nivolumab was stopped, and his vision function stabilized after a 2-year follow-up.

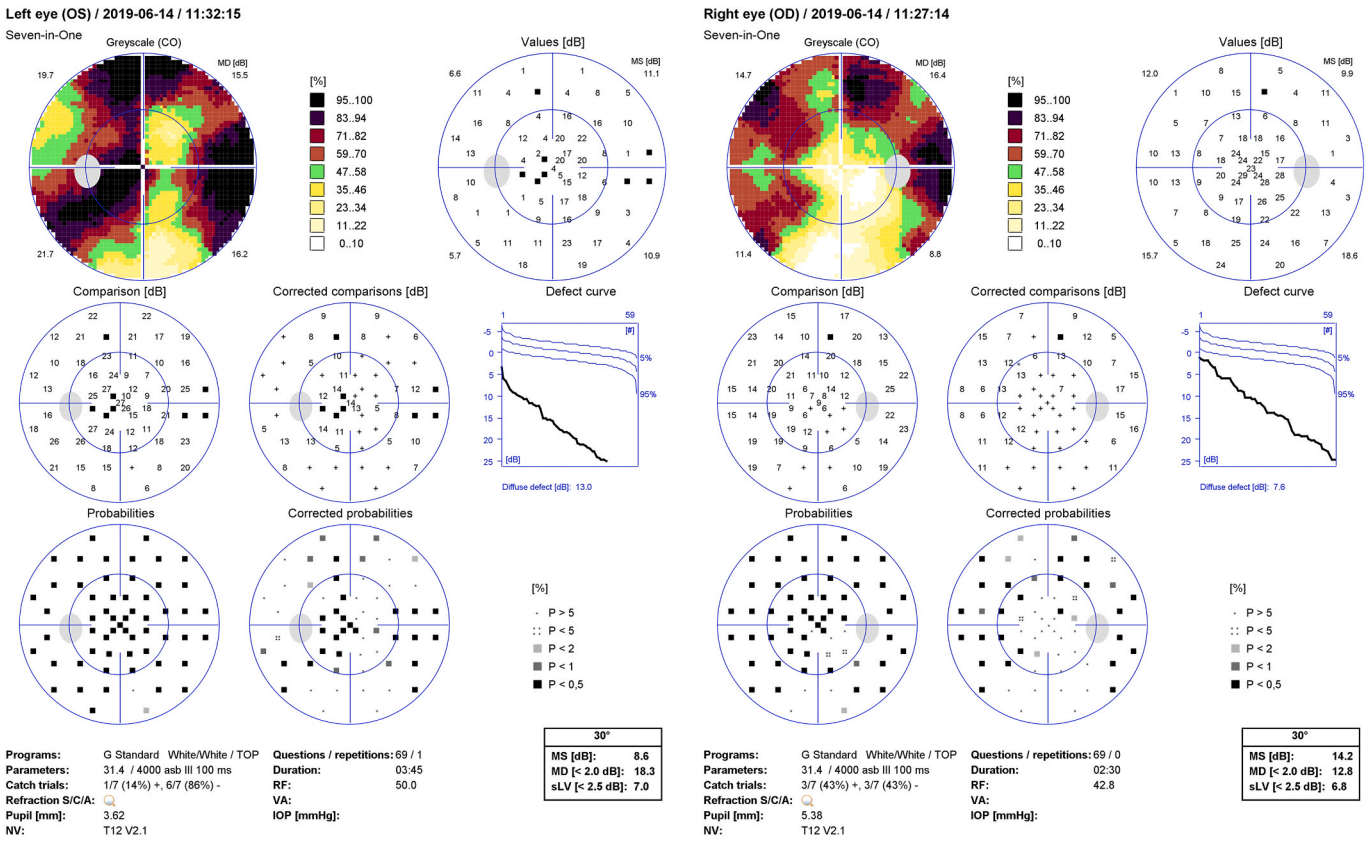

Fig. 2. Octopus visual field testing at acute onset showing a peripheral defect in the right eye and ring scotoma in the left eye.

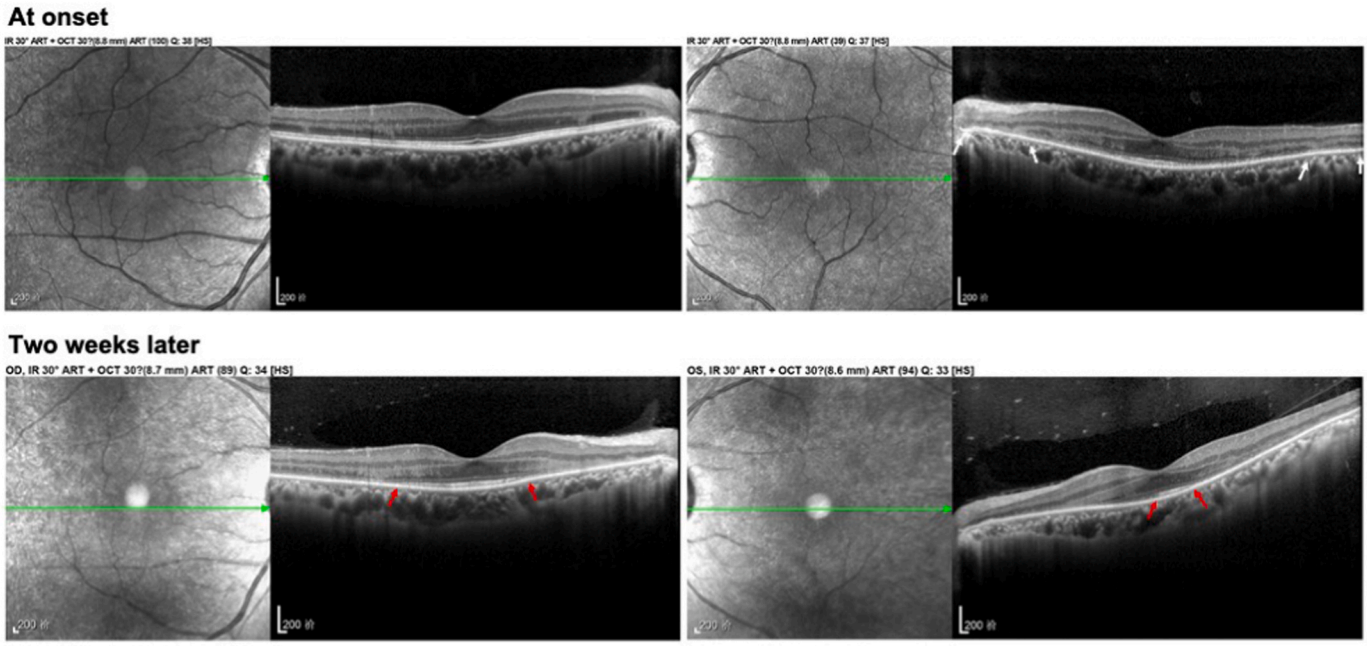

Fig. 3. Optical coherence tomography of a patient with cancer-associated retinopathy after anti-programmed death 1 (PD-1) antibody showing progressive photoreceptor disruption. Upper panel: normal ellipsoid zone of the macula in the right eye and disruption of the ellipsoid in the left eye at onset; white arrows indicate loss of the outer nuclear layer of the retina. Lower panel: 2 weeks later, photoreceptors at the maculae show an extensive loss. Areas between the red arrows indicate the remains of the normal ellipsoid zone under the maculae. There are inflammatory vitreous cells in both eyes but more severe in the left eye. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

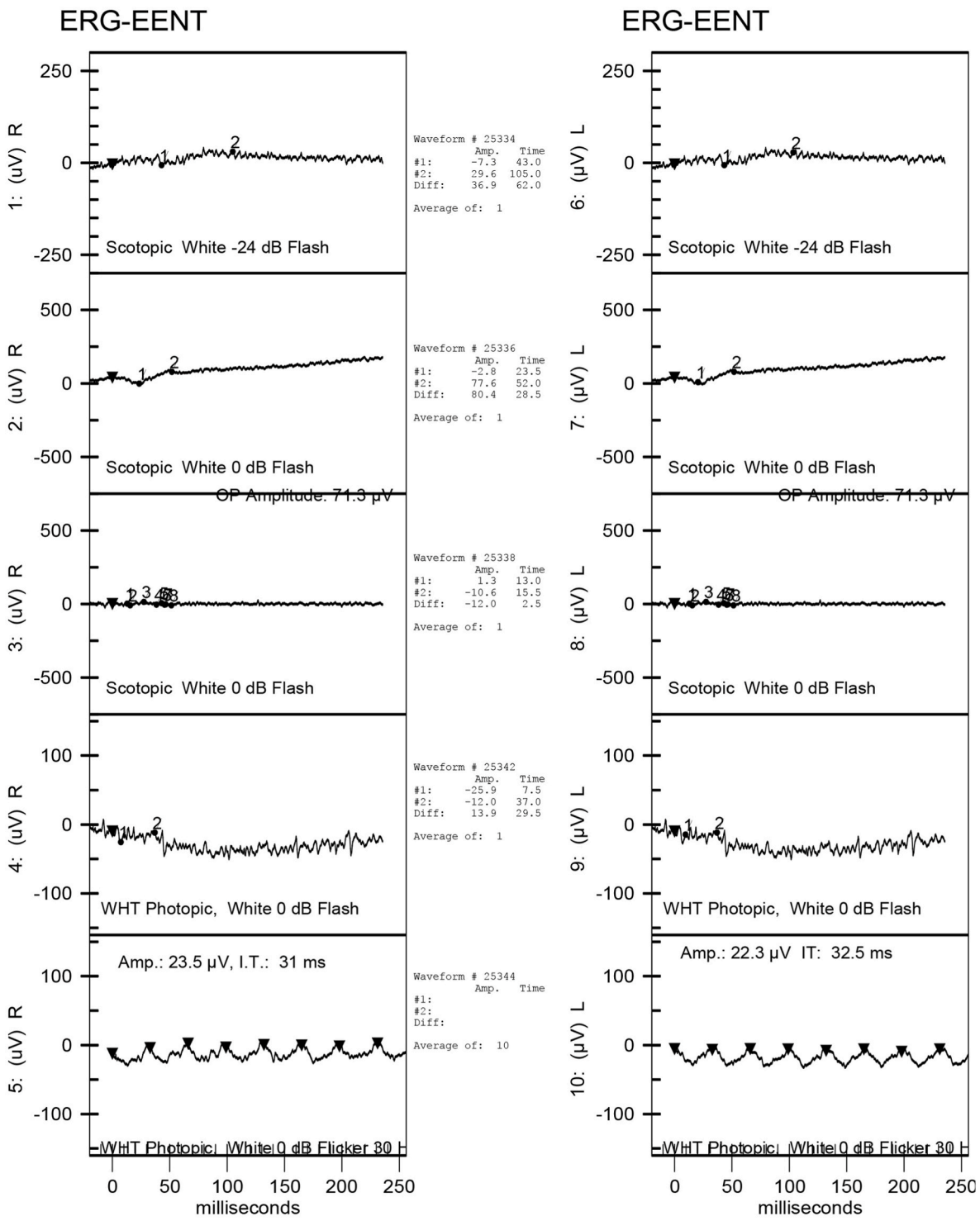

Fig. 4. Full-field electroretinography showing almost extinguished scotopic and photopic responses of the bilateral retinas.

3. Discussion

Ophthalmic side effects are an increasingly recognized consequence of the use of anti-PD-1 antibodies in the treatment of solid-organ tumors. The most frequent manifestations are uveitis, dry eye, keratitis, optic neuropathy, and immune retinopathy.[1–3] Anti-PD-1 treatment activates T-cells to attack tumor cells which in turn can also induce CAR. The reasons supporting that the autoimmune retinopathy was induced by anti-PD-1 therapy were as follows. First, the patient never reported visual problems prior to nivolumab treatment, and his annual routine eye examination showed no obvious abnormalities. Second, the patient's hepatocellular carcinoma had been well-controlled after chemotherapy, whereas the retinopathy worsened quickly. After nivolumab was stopped, the patient had been followed up for more than two years with stable visual function. As we know, most cases of paraneoplastic autoimmune retinopathy are due to small-cell lung carcinoma and ovarian and breast malignancies and less commonly due to non-small-cell lung, prostate, thymus, thyroid, and pancreatic cancers.[4–7] Hepatocellular carcinoma leading to paraneoplastic autoimmune retinopathy was reported only in the following two patients: one was diagnosed with CAR

and another with bilateral diffuse uveal melanocytic proliferation.[8,9] The high serum titer of anti-recoverin antibody in our patient detected after nivolumab therapy indicates that the excessive T-cell response (along with B cells and natural killer cells) might lead to an overproduction of anti-retinal antibodies, such as anti-recoverin, which attack photoreceptor cells.

Although visual prognosis with CAR is generally poor despite various immunosuppressive therapies, some reports showed favorable outcomes after systemic steroids.[10,11] High-dose intravenous methylprednisolone has resulted in mild-to-moderate improvement in visual acuity and visual fields, more so than oral prednisone.[12]

With the wide use of immune checkpoint inhibitor therapy for solid-organ tumors, we suggest that baseline ophthalmic examinations, including OCT, are crucial prior to nivolumab treatment.

4. Conclusion

Anti-PD-1 therapy for solid tumors might induce autoimmune retinopathies related to some paraneoplastic antibodies like recoverin. Testing of serum paraneoplastic antibodies, together with OCT and ERG examination, will help to diagnose this disorder.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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Authors' contributions

Involved in design of study (GHT, WJW); conduct of the study (CBS, MW, LC); data collection (QC and CYF); analysis and interpretation (QC and GHT); funding acquisition (XHS); preparation and revision of the manuscript (QC and CYF); final approval of the article (GHT). All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no competing interests.

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Not applicable.

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