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

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A B S T R A C T
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
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,
one 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 exami-
nation 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.

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, Koniz, 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 mag-
netic resonance imaging with contrast showed normal bilateral optic
nerves without enhancement and no other remarkable findings. Fluo-
rescein 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 un-
changed. Nivolumab was stopped, and his vision function stabilized
after a 2-year follow-up.

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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.
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.)
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. 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. 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.\textsuperscript{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.\textsuperscript{10,11} High-dose intravenous methylprednisolone has resulted in mild-to-moderate improvement in visual acuity and visual fields, more so than oral prednisone.\textsuperscript{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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References

1. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA.Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina. 2018 Jun;38(6):1063–1078.
2. Costa R, Carneiro BA, Agulnik M, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget. 2017 Jan 31;8(5):8910–8920.
3. Kao JC, Liao B, Markovic SN, et al. Neurological complications associated with anti-programmed death 1 (PD-1) antibodies. JAMA Neurol. 2017 Oct 17;74(10):1216–1222.
4. Adamas G, Champaigne R, Yang S. Occurrence of major anti-retinal autoantibodies associated with paraneoplastic autoimmune retinopathy. Clin Immunol. 2020;210:108317.
5. Grewal DS, Fishman GA, Jampol LM. Autoimmune retinopathy and antiretinal antibodies: a review. Retina. 2014 May;34(5):827–845.
6. Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management. Surv Ophthalmol. 2013 Sep-Oct;58(5):430–458.
7. Adamus G. Autoantibody targets and their cancer relationship in the pathogenicity of paraneoplastic retinopathy. Autoimmun Rev. 2009 Mar;8(5):410–414.
8. Chang PY, Yang CH, Yang CM. Cancer-associated retinopathy in a patient with hepatocellular carcinoma: case report and literature review. Retina. 2005 Dec;25(8):1093–1096.
9. Lee JM, Seong HK, Nam WH, Kim HK. Cancer-associated nummular loss of the retinal pigment epithelium. Kor J Ophthalmol. 2007 Dec;21(4):261–264.
10. Suimon Y, Saito W, Hirooka K, et al. Improvements of visual function and outer retinal morphology following spontaneous regression of cancer in anti-recoverin cancer-associated retinopathy. Am J Ophthalmol Case Rep. 2017 Jan 6;5:137–140.
11. Koyne-Guiboert F, Graus F, Fleury A, et al. Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (Anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. J Neurol Neurosurg Psychiatry. 2000 Apr;68(4):479–482.
12. Sen HN, Grange L, Akanda M, Fox A. Autoimmune retinopathy: current concepts and practices (an American ophthalmological society thesis). Trans Am Ophthalmol Soc. 2018 Mar 8:115. T8. eCollection 2017 Aug. Review.